

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
24 June 2004 (24.06.2004)

PCT

(10) International Publication Number  
**WO 2004/052858 A2**

(51) International Patent Classification<sup>7</sup>: **C07D 211/00**

(21) International Application Number:  
PCT/US2003/035972

(22) International Filing Date:  
25 November 2003 (25.11.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
0228482.6 6 December 2002 (06.12.2002) GB  
60/434,720 18 December 2002 (18.12.2002) US

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(81) Designated States (national): AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA,

CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, EG, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK (utility model), SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

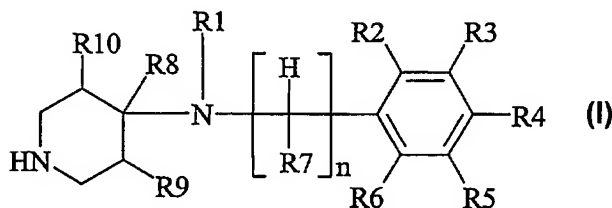
(84) Designated States (regional): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

#### Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM,

[Continued on next page]

(54) Title: INHIBITORS OF MONOAMINE UPTAKE



(57) Abstract: N,N-disubstituted 4-amino-piperidines of the general Formula (I) are inhibitors of the uptake of serotonin and/or norepinephrine and/or dopamine. As such, they may be useful for the treatment of disorders of the central and/or peripheral nervous system.



ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM,

ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

- of inventorship (Rule 4.17(iv)) for US only

**Published:**

- without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



## INHIBITORS OF MONOAMINE UPTAKE

The present invention is directed to compounds which inhibit the uptake of one or more physiologically active monoamines selected from serotonin (also called 5-hydroxytryptamine or 5-HT), norepinephrine (also called noradrenaline) and dopamine. There is a large body of scientific evidence pointing to the physiological role of these monoamines as neurotransmitters. Consequently, compounds which are capable of inhibiting the uptake of one or more of these monoamines find utility in the treatment of disorders of the central and/or peripheral nervous system.

It is known that the 3-aryloxy-3-substituted-1-aminopropane class of compounds have demonstrated particular diversity in their ability to inhibit the uptake of monoamines. Fluoxetine (N-methyl 3-((4-trifluoromethylphenyl)oxy)-3-phenyl-1-aminopropane hydrochloride), for example, is a selective serotonin uptake inhibitor that has found great market acceptance in the treatment of depression and has also been approved for the treatment of a number of other disorders. Atomoxetine ((-)-N-methyl 3-((2-methylphenyl)oxy)-3-phenyl-1-aminopropane hydrochloride), is a selective norepinephrine uptake inhibitor that is approved for the treatment of attention deficit/hyperactivity disorder. Duloxetine ((+)-N-methyl 3-(1-naphthalenyloxy)-3-(2-thienyl)-1-aminopropane hydrochloride), is a dual serotonin and norepinephrine uptake inhibitor that is in clinical development for the treatment of depression.

EP-A2-0112776 discloses the compound N-ethyl-N-benzyl-4-piperidinamine as an intermediate in the synthesis of naphthalene- or azanaphthalene-carboxamides.

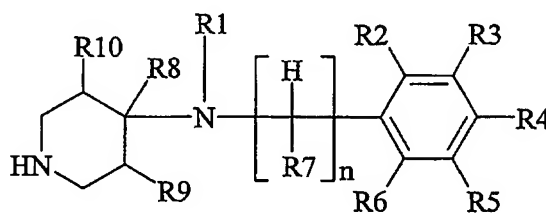
It would be advantageous to provide further compounds which are capable of inhibiting the uptake of one or more monoamines selected from serotonin, norepinephrine and dopamine. Preferably, such compounds would exhibit one or more of the following characteristics when compared with known monoamine uptake inhibitors – (i) improved potency in their inhibition of one or more of these monoamines, (ii) improved selectivity in their inhibition of one or more of these monoamines, (iii) improved bioavailability, (iv)

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minimal interaction with metabolic enzymes such as CYP2D6 and (v) improved acid stability.

Accordingly, the present invention provides a compound of formula I

5



I

wherein

n is 1, 2 or 3;

R1 is C<sub>2</sub>-C<sub>10</sub>alkyl, C<sub>2</sub>-C<sub>10</sub>alkenyl, C<sub>3</sub>-C<sub>8</sub>cycloalkyl or C<sub>4</sub>-C<sub>10</sub>cycloalkylalkyl, wherein

10 one C-C bond within any cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond and wherein each group is optionally substituted with from 1 to 7 halogen substituents and/or with from 1 to 3 substituents each independently selected from hydroxy, cyano, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkylthio (optionally substituted with from 1 to 3 halogen atoms) and C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 3 halogen atoms);

15 R2 is H, C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkyl-S(O)<sub>x</sub>- wherein x is 0, 1 or 2 (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy) or  
 20 -CO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), or together with R3 forms a further benzene ring (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy);

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- R3 is H, C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkyl-S(O)<sub>x</sub>- wherein x is 0, 1 or 2 (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy) or -CO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), or together with R2 or R4 forms a further benzene ring (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy);
- 10 R4 is H, C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkyl-S(O)<sub>x</sub>- wherein x is 0, 1 or 2 (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy) or -CO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), or together with R3 forms a further benzene ring (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy);
- 15 R5 is H, C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms) or halogen;
- 20 R6 is H, C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms) or halogen;
- R7 is H or C<sub>1</sub>-C<sub>4</sub>alkyl;
- R8 is H or C<sub>1</sub>-C<sub>4</sub>alkyl;
- 25 R9 is H, halogen, hydroxy, cyano, C<sub>1</sub>-C<sub>4</sub>alkyl or C<sub>1</sub>-C<sub>4</sub>alkoxy; and
- R10 is H, halogen, hydroxy, cyano, C<sub>1</sub>-C<sub>4</sub>alkyl or C<sub>1</sub>-C<sub>4</sub>alkoxy;
- or a pharmaceutically acceptable salt thereof,

with the proviso that the compound N-ethyl-N-benzyl-4-piperidinamine is excluded.

In a further embodiment, the present invention provides a compound of formula I above wherein

- 5 R1 is C<sub>2</sub>-C<sub>10</sub>alkyl, C<sub>2</sub>-C<sub>10</sub>alkenyl, C<sub>3</sub>-C<sub>8</sub>cycloalkyl or C<sub>4</sub>-C<sub>10</sub>cycloalkylalkyl, wherein one C-C bond within any cycloalkyl moiety is optionally substituted by an O-C or C=C bond and wherein each group is optionally substituted with from 1 to 7 halogen substituents and/or with from 1 to 3 substituents each independently selected from hydroxy, cyano, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy; and
- 10 n; R<sub>2</sub>; R<sub>3</sub>; R<sub>4</sub>; R<sub>5</sub>; R<sub>6</sub>; R<sub>7</sub>; R<sub>8</sub>; R<sub>9</sub>; and R<sub>10</sub> are as defined above;  
or a pharmaceutically acceptable salt thereof,  
with the proviso that the compound N-ethyl-N-benzyl-4-piperidinamine is excluded.

- In the present specification the term "C<sub>2</sub>-C<sub>10</sub>alkyl" means a monovalent unsubstituted
- 15 saturated straight-chain or branched-chain hydrocarbon radical having from 2 to 10 carbon atoms.

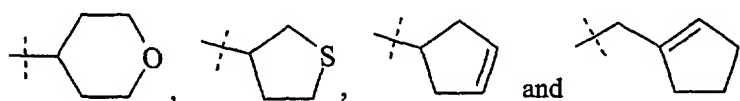
- In the present specification the term "C<sub>2</sub>-C<sub>10</sub>alkenyl" means a monovalent unsubstituted
- unsaturated straight-chain or branched-chain hydrocarbon radical having from 2 to 10
- 20 carbon atoms and containing at least one carbon-carbon double bond.

In the present specification the term "C<sub>3</sub>-C<sub>8</sub>cycloalkyl" means a monovalent unsubstituted saturated cyclic hydrocarbon radical having from 3 to 8 carbon atoms.

- 25 In the present specification the term "C<sub>4</sub>-C<sub>10</sub>cycloalkylalkyl" means a monovalent unsubstituted saturated cyclic hydrocarbon radical having from 3 to 9 carbon atoms linked to the point of substitution by a divalent unsubstituted saturated straight-chain or branched-chain hydrocarbon radical having at least 1 carbon atom.

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In the present specification the phrase “wherein one C-C bond within any cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond” means that either (i) any two adjacent carbon atoms within a cycloalkyl ring may be linked by a double bond rather than a single bond (with the number of substituents on each carbon atom being reduced accordingly), or that (ii) one of any two adjacent C atoms within a cycloalkyl ring (and any substituents thereon) may be replaced by an oxygen or sulphur atom. Examples of R1 groups encompassed by this phrase include but are not limited to:



10 In the present specification the term “halo” or “halogen” means F, Cl, Br or I.

In the present specification the term “C<sub>1</sub>-C<sub>4</sub>alkylthio” means a monovalent unsubstituted saturated straight-chain or branched-chain hydrocarbon radical having from 1 to 4 carbon atoms linked to the point of substitution by a S atom.

15

In the present specification the term “C<sub>1</sub>-C<sub>4</sub>alkoxy” means a monovalent unsubstituted saturated straight-chain or branched-chain hydrocarbon radical having from 1 to 4 carbon atoms linked to the point of substitution by an O atom.

20 In the present specification the term “phenoxy” means a monovalent unsubstituted phenyl radical linked to the point of substitution by an O atom.

In the above definitions, similar terms specifying different numbers of C atoms take an analogous meaning.

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In a preferred embodiment, n is 1 or 2. More preferably, n is 1.

In a preferred embodiment, R7 is H or methyl. More preferably R7 is H.

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In a preferred embodiment, R8 is H.

In a preferred embodiment, R9 is H or fluoro. More preferably, R9 is H.

5 In a preferred embodiment, R10 is H or fluoro. More preferably, R10 is H.

In a preferred embodiment, R1 is C<sub>2</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl or C<sub>4</sub>-C<sub>7</sub>cycloalkylalkyl, wherein one C-C bond within any cycloalkyl moiety is optionally substituted by an O-C bond and wherein each group is optionally substituted with from 1  
10 to 3 halogen atoms or a hydroxy, cyano, C<sub>1</sub>-C<sub>4</sub>alkylthio (optionally substituted with from 1 to 3 halogen atoms) or C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 3 halogen atoms) radical. More preferably, R1 is C<sub>2</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl or C<sub>4</sub>-C<sub>7</sub>cycloalkylalkyl, wherein one C-C bond within any cycloalkyl moiety is optionally substituted by an O-C bond and wherein each group is optionally substituted with from 1  
15 to 3 halogen atoms or a hydroxy, cyano, methylthio, methoxy, trifluoromethoxy, ethoxy, or isopropoxy radical. More preferably, R1 is C<sub>2</sub>-C<sub>6</sub>alkyl (optionally substituted with from 1 to 3 halogen atoms or a hydroxy, cyano, methylthio, methoxy, trifluoromethoxy, ethoxy, or isopropoxy radical), C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl or C<sub>4</sub>-C<sub>7</sub>cycloalkylalkyl (optionally substituted with a halogen atom or hydroxy radical), wherein one C-C bond  
20 within any cycloalkyl moiety is optionally substituted by an O-C bond. Suitable C<sub>2</sub>-C<sub>6</sub>alkyl groups (optionally substituted with from 1 to 3 halogen atoms or a hydroxy, cyano, methylthio, methoxy, trifluoromethoxy, ethoxy, or isopropoxy radical) include, for example, ethyl, 2-cyanoethyl, 2-hydroxyethyl, 2-methoxyethyl, 2-trifluoromethoxyethyl, 2-methylthioethyl, 2-ethoxyethyl, 2-isopropoxyethyl, 2,2,2-trifluoroethyl, n-propyl, ,  
25 isopropyl, 3-methoxypropyl, 3-hydroxypropyl, 3-cyanopropyl, 3,3,3-trifluoropropyl, n-butyl, isobutyl, 4-methoxybutyl, 4,4,4-trifluorobutyl, 2-methoxy-2-methylpropyl, 2-hydroxy-2-methylpropyl, 2-cyano-2-methylpropyl, n-pentyl, 3-methylbutyl, 3-cyano-3-methylbutyl, 3-hydroxy-3-methylbutyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 2,2-dimethyl-3-hydroxypropyl, 1-ethylpropyl, 3,3-dimethylbutyl, 2-ethylbutyl and 2-

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methylpentyl. Suitable C<sub>2</sub>-C<sub>6</sub>alkenyl groups include, for example, 2-methyl-2-propenyl. Suitable C<sub>3</sub>-C<sub>6</sub>cycloalkyl groups wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C bond include, for example, cyclopentyl and tetrahydro-2H-pyran-4-yl. Suitable C<sub>4</sub>-C<sub>7</sub>cycloalkylalkyl groups (optionally substituted with a

5 halogen atom or hydroxy radical) wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C bond include, for example, cycloheptylmethyl, cyclohexylmethyl, tetrahydro-2H-pyran-4-ylmethyl, cyclopentylmethyl, hydroxycyclopentylmethyl, cyclobutylmethyl, cyclopropylmethyl and fluorocyclopropylmethyl.

10

In another preferred embodiment, R<sub>1</sub> is C<sub>2</sub>-C<sub>6</sub>alkyl, C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl or C<sub>4</sub>-C<sub>7</sub>cycloalkylalkyl, each of which is optionally substituted with from 1 to 3 halogen atoms or a methoxy radical. More preferably, R<sub>1</sub> is C<sub>2</sub>-C<sub>6</sub>alkyl (optionally substituted with from 1 to 3 halogen atoms or a methoxy radical), C<sub>2</sub>-C<sub>6</sub>alkenyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl or

15 C<sub>4</sub>-C<sub>7</sub>cycloalkylalkyl. Suitable C<sub>2</sub>-C<sub>6</sub>alkyl groups (optionally substituted with from 1 to 3 halogen atoms or a methoxy radical) include, for example, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-pentyl, 3-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, 3,3-dimethylbutyl, 2-ethylbutyl, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl and 2-methoxyethyl. Suitable C<sub>2</sub>-C<sub>6</sub>alkenyl groups include, for example, 2-methyl-2-propenyl.

20 Suitable C<sub>3</sub>-C<sub>6</sub>cycloalkyl groups include, for example, cyclopentyl. Suitable C<sub>4</sub>-C<sub>7</sub>cycloalkylalkyl groups include, for example, cyclohexylmethyl or cyclopropylmethyl.

In another preferred embodiment, R<sub>1</sub> is a C<sub>2</sub>-C<sub>10</sub>alkyl group optionally substituted with from 1 to 7 halogen substituents and/or with from 1 to 3 substituents each independently

25 selected from hydroxy, cyano, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkylthio (optionally substituted with from 1 to 3 halogen atoms) and C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 3 halogen atoms). More preferably, R<sub>1</sub> is a C<sub>2</sub>-C<sub>10</sub>alkyl group optionally substituted with from 1 to 7 halogen substituents and/or with from 1 to 3 substituents each independently selected from hydroxy, cyano, C<sub>1</sub>-C<sub>4</sub>alkylthio (optionally substituted with from 1 to 3

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halogen atoms) and C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 3 halogen atoms). More preferably, R<sub>1</sub> is a C<sub>2</sub>-C<sub>10</sub>alkyl group optionally substituted with from 1 to 3 substituents each independently selected from halogen, hydroxy, cyano, C<sub>1</sub>-C<sub>4</sub>alkylthio and C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 3 fluorine atoms). More

5 preferably R<sub>1</sub> is C<sub>2</sub>-C<sub>6</sub>alkyl optionally substituted with from 1 to 3 halogen atoms or a hydroxy, cyano, methylthio, methoxy, trifluoromethoxy, ethoxy, or isopropoxy radical. Still more preferably R<sub>1</sub> is C<sub>2</sub>-C<sub>6</sub>alkyl optionally substituted with from 1 to 3 fluorine atoms or a hydroxy, cyano, methylthio, methoxy, trifluoromethoxy, ethoxy, or isopropoxy radical. Still more preferably, R<sub>1</sub> is selected from ethyl, 2-cyanoethyl, 2-hydroxyethyl, 2-methoxyethyl, 2-trifluoromethoxyethyl, 2-methylthioethyl, 2-ethoxyethyl, 2-isopropoxyethyl, 2,2,2-trifluoroethyl, n-propyl, isopropyl, 3-methoxypropyl, 3-hydroxypropyl, 3-cyanopropyl, 3,3,3-trifluoropropyl, n-butyl, isobutyl, 4-methoxybutyl, 4,4,4-trifluorobutyl, 2-methoxy-2-methylpropyl, 2-hydroxy-2-methylpropyl, 2-cyano-2-methylpropyl, n-pentyl, 3-methylbutyl, 3-cyano-3-methylbutyl, 3-hydroxy-3-methylbutyl, 15 1,2-dimethylpropyl, 2,2-dimethylpropyl, 2,2-dimethyl-3-hydroxypropyl, 1-ethylpropyl, 3,3-dimethylbutyl, 2-ethylbutyl and 2-methylpentyl. Most preferably R<sub>1</sub> is selected from n-propyl, n-butyl, isobutyl, 3-methoxypropyl, 3-hydroxypropyl, 3-cyanopropyl, 4-methoxybutyl, 2-hydroxy-2-methylpropyl, 2-cyano-2-methylpropyl, 3-hydroxy-2,2-dimethylpropyl and 3-cyano-3-methylbutyl.

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In another preferred embodiment, R<sub>1</sub> is a C<sub>2</sub>-C<sub>10</sub>alkyl group optionally substituted with from 1 to 7 halogen substituents and/or with from 1 to 3 substituents each independently selected from hydroxy, cyano and C<sub>1</sub>-C<sub>4</sub>alkoxy. More preferably, R<sub>1</sub> is a C<sub>2</sub>-C<sub>10</sub>alkyl group optionally substituted with from 1 to 3 substituents each independently selected from halogen, hydroxy and C<sub>1</sub>-C<sub>4</sub>alkoxy. More preferably R<sub>1</sub> is C<sub>2</sub>-C<sub>6</sub>alkyl optionally substituted with from 1 to 3 halogen atoms or a methoxy radical. Still more preferably R<sub>1</sub> is C<sub>2</sub>-C<sub>6</sub>alkyl. Still more preferably, R<sub>1</sub> is selected from ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-pentyl, 3-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, 3,3-dimethylbutyl and 2-ethylbutyl. Most preferably R<sub>1</sub> is selected from n-propyl, n-butyl and isobutyl.

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In another preferred embodiment, R1 is a C<sub>2</sub>-C<sub>10</sub>alkenyl group optionally substituted with from 1 to 7 halogen substituents and/or with from 1 to 3 substituents each independently selected from hydroxy, cyano, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkylthio (optionally substituted with from 1 to 3 halogen atoms) and C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with  
5 from 1 to 3 halogen atoms). More preferably, R1 is a C<sub>2</sub>-C<sub>10</sub>alkenyl group optionally substituted with from 1 to 7 halogen substituents and/or with from 1 to 3 substituents each independently selected from hydroxy, cyano, C<sub>1</sub>-C<sub>4</sub>alkylthio (optionally substituted with from 1 to 3 halogen atoms) and C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 3  
10 halogen atoms). More preferably, R1 is a C<sub>2</sub>-C<sub>10</sub>alkenyl group optionally substituted with from 1 to 3 substituents each independently selected from halogen, hydroxy, cyano, C<sub>1</sub>-C<sub>4</sub>alkylthio and C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 3 fluorine atoms). More preferably R1 is C<sub>2</sub>-C<sub>6</sub>alkenyl optionally substituted with from 1 to 3 halogen atoms or a hydroxy, cyano, methylthio, methoxy, trifluoromethoxy, ethoxy, or isopropoxy radical. Still more preferably R1 is C<sub>2</sub>-C<sub>6</sub>alkenyl. Still more preferably, R1 is  
15 2-methyl-2-propenyl.

In another preferred embodiment, R1 is a C<sub>3</sub>-C<sub>8</sub>cycloalkyl group, wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond and wherein the group is optionally substituted with from 1 to 7 halogen substituents and/or  
20 with from 1 to 3 substituents each independently selected from hydroxy, cyano, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkylthio (optionally substituted with from 1 to 3 halogen atoms) and C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 3 halogen atoms). More preferably, R1 is a C<sub>3</sub>-C<sub>8</sub>cycloalkyl group, wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond. More preferably, R1 is a C<sub>4</sub>-  
25 C<sub>6</sub>cycloalkyl group, wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond. Still more preferably, R1 is cyclopentyl or tetrahydro-2H-pyran-4-yl

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In another preferred embodiment, R1 is a C<sub>4</sub>-C<sub>10</sub>cycloalkylalkyl group, wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond and wherein the group is optionally substituted with from 1 to 7 halogen substituents and/or with from 1 to 3 substituents each independently selected from hydroxy, cyano, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkylthio (optionally substituted with from 1 to 3 halogen atoms) and C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 3 halogen atoms). More preferably, R1 is a C<sub>4</sub>-C<sub>10</sub>cycloalkylalkyl group, wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond and wherein the group is optionally substituted with from 1 to 3 substituents each independently selected from halogen, hydroxy, cyano, C<sub>1</sub>-C<sub>2</sub>alkyl, C<sub>1</sub>-C<sub>2</sub>alkylthio (optionally substituted with from 1 to 3 halogen atoms) and C<sub>1</sub>-C<sub>2</sub>alkoxy (optionally substituted with from 1 to 3 halogen atoms). More preferably, R1 is a C<sub>4</sub>-C<sub>7</sub>cycloalkylalkyl group (optionally substituted with a halogen atom or hydroxy radical) wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C bond. Still more preferably, R1 is cycloheptylmethyl, cyclohexylmethyl, tetrahydro-2H-pyran-4-ylmethyl, cyclopentylmethyl, hydroxycyclopentylmethyl, cyclobutylmethyl, cyclopropylmethyl or fluorocyclopropylmethyl.

In a preferred embodiment, R2 is H, C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkyl-S(O)<sub>x</sub>- wherein x is 0 or 2 (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy) or phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy), or together with R3 forms a further benzene ring (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy). More preferably, R2 is H, C<sub>1</sub>-C<sub>2</sub>alkyl (optionally substituted with from 1 to 5 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkyl-S(O)<sub>x</sub>- wherein x is 0 or 2 (optionally substituted with from 1 to 5 halogen atoms), C<sub>1</sub>-C<sub>2</sub>alkoxy (optionally

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substituted with from 1 to 5 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>2</sub>alkyl and C<sub>1</sub>-C<sub>2</sub>alkoxy) or phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>2</sub>alkyl and C<sub>1</sub>-C<sub>2</sub>alkoxy), or  
5 together with R<sub>3</sub> forms a further benzene ring (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>2</sub>alkyl and C<sub>1</sub>-C<sub>2</sub>alkoxy).  
Still more preferably, R<sub>2</sub> is H, methyl, trifluoromethyl, methylthio, tert-butylthio, trifluoromethylthio, methylsulfonyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, cyano, fluoro, chloro, bromo, phenyl or phenoxy, or together with R<sub>3</sub>  
10 forms a further benzene ring.

In another preferred embodiment, R<sub>2</sub> is not H. More preferably, R<sub>2</sub> is C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkyl-S(O)<sub>x</sub>- wherein x is 0 or 2 (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy) or phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy), or  
15 together with R<sub>3</sub> forms a further benzene ring (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy).  
More preferably, R<sub>2</sub> is C<sub>1</sub>-C<sub>2</sub>alkyl (optionally substituted with from 1 to 5 halogen atoms), C<sub>1</sub>-C<sub>2</sub>alkyl-S(O)<sub>x</sub>- wherein x is 0 or 2 (optionally substituted with from 1 to 5 halogen atoms), C<sub>1</sub>-C<sub>2</sub>alkoxy (optionally substituted with from 1 to 5 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each  
25 independently selected from halogen, C<sub>1</sub>-C<sub>2</sub>alkyl and C<sub>1</sub>-C<sub>2</sub>alkoxy) or phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>2</sub>alkyl and C<sub>1</sub>-C<sub>2</sub>alkoxy), or together with R<sub>3</sub> forms a further benzene ring (optionally substituted with from 1 to 3 substituents each independently selected from

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halogen, C<sub>1</sub>-C<sub>2</sub>alkyl and C<sub>1</sub>-C<sub>2</sub>alkoxy). Still more preferably, R<sub>2</sub> is methyl, trifluoromethyl, methylthio, tert-butylthio, trifluoromethylthio, methylsulfonyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, cyano, fluoro, chloro, bromo, phenyl or phenoxy, or together with R<sub>3</sub> forms a further benzene ring.

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In a preferred embodiment, R<sub>3</sub> is H, C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkyl-S- (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy) or -CO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), or together with R<sub>2</sub> or R<sub>4</sub> forms a further benzene ring (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy). More preferably, R<sub>3</sub> is H, C<sub>1</sub>-C<sub>2</sub>alkyl (optionally substituted with from 1 to 5 halogen atoms), C<sub>1</sub>-C<sub>2</sub>alkyl-S- (optionally substituted with from 1 to 5 halogen atoms), C<sub>1</sub>-C<sub>2</sub>alkoxy (optionally substituted with from 1 to 5 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>2</sub>alkyl and C<sub>1</sub>-C<sub>2</sub>alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>2</sub>alkyl and C<sub>1</sub>-C<sub>2</sub>alkoxy) or -CO<sub>2</sub>(C<sub>1</sub>-C<sub>2</sub>alkyl), or together with R<sub>2</sub> or R<sub>4</sub> forms a further benzene ring (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>2</sub>alkyl and C<sub>1</sub>-C<sub>2</sub>alkoxy). Still more preferably, R<sub>3</sub> is H, methyl, trifluoromethyl, trifluoromethylthio, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, cyano, fluoro, chloro, bromo, phenyl, phenoxy or CO<sub>2</sub>CH<sub>3</sub>, or together with R<sub>2</sub> or R<sub>4</sub> forms a further benzene ring.

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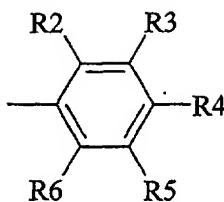
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In a preferred embodiment, R<sub>4</sub> is H, C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkyl-S- (optionally substituted with from 1 to 7 halogen atoms),

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- C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy), or -CO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), or together with R<sub>3</sub> forms a further benzene ring (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy). More preferably, R<sub>4</sub> is H, C<sub>1</sub>-C<sub>2</sub>alkyl (optionally substituted with from 1 to 5 halogen atoms), C<sub>1</sub>-C<sub>2</sub>alkyl-S- (optionally substituted with from 1 to 5 halogen atoms), C<sub>1</sub>-C<sub>2</sub>alkoxy (optionally substituted with from 1 to 5 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>2</sub>alkyl and C<sub>1</sub>-C<sub>2</sub>alkoxy), or -CO<sub>2</sub>(C<sub>1</sub>-C<sub>2</sub>alkyl), or together with R<sub>3</sub> forms a further benzene ring (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>2</sub>alkyl and C<sub>1</sub>-C<sub>2</sub>alkoxy). Still more preferably, R<sub>4</sub> is H, methyl, trifluoromethyl, methylthio, methoxy, trifluoromethoxy, cyano, fluoro, chloro, phenyl or CO<sub>2</sub>CH<sub>3</sub>, or together with R<sub>3</sub> forms a further benzene ring.
- In a preferred embodiment, R<sub>5</sub> is H, C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 5 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 5 halogen atoms) or halogen. More preferably, R<sub>5</sub> is H, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkoxy or halogen. Still more preferably, R<sub>5</sub> is H, methyl, methoxy, fluoro or chloro.
- In a preferred embodiment, R<sub>6</sub> is H, C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 5 halogen atoms) or halogen. More preferably, R<sub>6</sub> is H, C<sub>1</sub>-C<sub>4</sub>alkyl or halogen. Still more preferably, R<sub>6</sub> is H, methyl, fluoro or chloro.
- In a further preferred embodiment of the present invention, the group

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is phenyl, 2-methylphenyl, 2-(trifluoromethyl)phenyl, 2-(methylthio)phenyl, 2-(tertbutylthio)phenyl, 2-(trifluoromethylthio)phenyl, 2-(methylsulfonyl)phenyl, 2-methoxyphenyl, 2-ethoxyphenyl, 2-(difluoromethoxy)phenyl, 2-(trifluoromethoxy)phenyl, 2-cyanophenyl, 2-fluorophenyl, 2-chlorophenyl, 2-bromophenyl, 2-biphenyl, 2-phenoxyphenyl, 3-methylphenyl, 3-(trifluoromethyl)phenyl, 3-(trifluoromethylthio)phenyl, 3-methoxyphenyl, 3-ethoxyphenyl, 3-(difluoromethoxy)phenyl, 3-(trifluoromethoxy)phenyl, 3-cyanophenyl, 3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 3-biphenyl, 3-phenoxyphenyl, 3-(methoxycarbonyl)phenyl, 4-methylphenyl, 4-(trifluoromethyl)phenyl, 4-(methylthio)phenyl, 4-methoxyphenyl, 4-(trifluoromethoxy)phenyl, 4-cyanophenyl, 4-fluorophenyl, 4-chlorophenyl, 4-biphenyl, 4-(methoxycarbonyl)phenyl, 2,3-dichlorophenyl, 2-chloro-3-methylphenyl, 2-chloro-3-(trifluoromethyl)phenyl, 2,4-dimethylphenyl, 2,4-bis(trifluoromethyl)phenyl, 2,4-dimethoxyphenyl, 2,4-difluorophenyl, 2,4-dichlorophenyl, 2-chloro-4-fluorophenyl, 2-fluoro-4-(trifluoromethyl)phenyl, 2-chloro-4-(methylsulfonyl)phenyl, 2,5-dimethylphenyl, 2,5-dichlorophenyl, 2-chloro-5-(trifluoromethyl)phenyl, 2,6-dimethylphenyl, 2,6-dichlorophenyl, 2-chloro-6-fluorophenyl, 2-fluoro-6-(trifluoromethyl)phenyl, 3-chloro-2-methylphenyl, 3-chloro-2-fluorophenyl, 3-chloro-2-(trifluoromethyl)phenyl, 3,4-dichlorophenyl, 3-chloro-4-fluorophenyl, 3,5-dimethylphenyl, 3,5-dimethoxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3-fluoro-5-(trifluoromethyl)phenyl, 5-fluoro-2-(trifluoromethylphenyl), 5-fluoro-2-methoxyphenyl, 4-fluoro-2-(trifluoromethyl)phenyl, 4-chloro-3-(trifluoromethyl)phenyl, 2,3,6-trichlorophenyl, 2,3,5-trichlorophenyl, 3-chloro-2-fluoro-6-(trifluoromethyl)phenyl, 3-chloro-2-fluoro-5-(trifluoromethyl)phenyl, 2-chloro-6-fluoro-3-methylphenyl, 2-chloro-6-fluoro-5-methylphenyl, 1-naphthyl or 2-naphthyl.

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A further embodiment of the present invention provides a group (Group A) of compounds of formula I above, wherein R2, R3, R4, R5 and R6 are all H.

5 A further embodiment of the present invention provides a group (Group B) of compounds of formula I above, wherein one of R2, R3, R4, R5 and R6 is not H and the others are H.

Compounds of Group B include those (Group B2) wherein R3, R4, R5 and R6 are all H and R2 is C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkyl-S(O)<sub>x</sub>- wherein x is 0,1 or 2 (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy) or -CO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl).

15 Compounds of Group B also include those (Group B3) wherein R2, R4, R5 and R6 are all H and R3 is C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkyl-S(O)<sub>x</sub>- wherein x is 0,1 or 2 (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy) or -CO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl).

25 Compounds of Group B also include those (Group B4) wherein R2, R3, R5 and R6 are all H and R4 is C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkyl-S(O)<sub>x</sub>- wherein x is 0,1 or 2 (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently

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selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy) or -CO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl).

- 5 A further embodiment of the present invention provides a group (Group C) of compounds of formula I above, wherein two of R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are not H and the others are H.

- Compounds of Group C include those (Group C<sub>2,3</sub>) wherein R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are all H; R<sub>2</sub> is C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkyl-  
10 S(O)<sub>x</sub>- wherein x is 0,1 or 2 (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy) or  
15 -CO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), or together with R<sub>3</sub> forms a further benzene ring (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy); and  
R<sub>3</sub> is C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkyl-  
S(O)<sub>x</sub>- wherein x is 0,1 or 2 (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-  
20 C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy) or  
-CO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), or together with R<sub>2</sub> forms a further benzene ring (optionally  
25 substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy).



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Compounds of Group C also include those (Group C2,4) wherein R3, R5 and R6 are all H;

- R2 is C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkyl-S(O)<sub>x</sub>- wherein x is 0,1 or 2 (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy) or -CO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl); and
- 10 R4 is C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkyl-S(O)<sub>x</sub>- wherein x is 0,1 or 2 (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy) or
- 15 -CO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl).

Compounds of Group C also include those (Group C2,5) wherein R3, R4 and R6 are all H;

- 20 R2 is C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkyl-S(O)<sub>x</sub>- wherein x is 0,1 or 2 (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy) or
- 25 -CO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl); and
- R5 is C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms) or halogen.

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Compounds of Group C also include those (Group C2,6) wherein R3, R4 and R5 are all H;

R2 is C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkyl-

5 S(O)<sub>x</sub>- wherein x is 0,1 or 2 (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy) or  
10 -CO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl); and

R6 is C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms) or halogen.

Compounds of Group C also include those (Group C3,4) wherein R2, R5 and R6 are all  
15 H;

R3 is C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkyl-

S(O)<sub>x</sub>- wherein x is 0,1 or 2 (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl

(optionally substituted with from 1 to 3 substituents each independently selected from

20 halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy) or -CO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), or together with R4 forms a further benzene ring (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy); and

25 R4 is C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkyl-

S(O)<sub>x</sub>- wherein x is 0,1 or 2 (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl

(optionally substituted with from 1 to 3 substituents each independently selected from

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halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy) or -CO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), or together with R<sub>3</sub> forms a further benzene ring (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy).

Compounds of Group C also include those (Group C<sub>3,5</sub>) wherein R<sub>2</sub>, R<sub>4</sub> and R<sub>6</sub> are all H;  
R<sub>3</sub> is C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkyl-S(O)<sub>x</sub>- wherein x is 0,1 or 2 (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy) or -CO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl); and  
R<sub>5</sub> is C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms) or halogen.

A further embodiment of the present invention provides a group (Group D) of compounds of formula I above, wherein three of R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are not H and the others are H.

Compounds of Group D include those (Group D<sub>2,3,5</sub>) wherein R<sub>4</sub> and R<sub>6</sub> are both H;  
R<sub>2</sub> is C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkyl-S(O)<sub>x</sub>- wherein x is 0,1 or 2 (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy), phenoxy (optionally substituted with from 1 to 3

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substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy) or -CO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), or together with R<sub>3</sub> forms a further benzene ring (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy);

- 5 R<sub>3</sub> is C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkyl-S(O)<sub>x</sub>- wherein x is 0,1 or 2 (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy) or  
10 -CO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), or together with R<sub>2</sub> forms a further benzene ring (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy); and  
R<sub>5</sub> is C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy  
15 (optionally substituted with from 1 to 7 halogen atoms) or halogen.

- Compounds of Group D include those (Group D<sub>2,3,6</sub>) wherein R<sub>4</sub> and R<sub>5</sub> are both H; R<sub>2</sub> is C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkyl-S(O)<sub>x</sub>- wherein x is 0,1 or 2 (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl  
20 (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy) or -CO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), or together with R<sub>3</sub> forms a further benzene ring (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy);  
25 R<sub>3</sub> is C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkyl-S(O)<sub>x</sub>- wherein x is 0,1 or 2 (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-

C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms), cyano, halogen, phenyl (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy), phenoxy (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy) or  
5 -CO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>alkyl), or together with R<sub>2</sub> forms a further benzene ring (optionally substituted with from 1 to 3 substituents each independently selected from halogen, C<sub>1</sub>-C<sub>4</sub>alkyl and C<sub>1</sub>-C<sub>4</sub>alkoxy); and  
R<sub>6</sub> is C<sub>1</sub>-C<sub>4</sub>alkyl (optionally substituted with from 1 to 7 halogen atoms), C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 7 halogen atoms) or halogen.

10

For compounds of Formula I falling within any one of groups A, B, B<sub>2</sub>, B<sub>3</sub>, B<sub>4</sub>, C, C<sub>2,3</sub>, C<sub>2,4</sub>, C<sub>2,5</sub>, C<sub>2,6</sub>, C<sub>3,4</sub>, C<sub>3,5</sub>, D, D<sub>2,3,5</sub> and D<sub>2,3,6</sub> described above, n is preferably 1 or 2, more preferably 1.

15 For compounds of Formula I falling within any one of groups A, B, B<sub>2</sub>, B<sub>3</sub>, B<sub>4</sub>, C, C<sub>2,3</sub>, C<sub>2,4</sub>, C<sub>2,5</sub>, C<sub>2,6</sub>, C<sub>3,4</sub>, C<sub>3,5</sub>, D, D<sub>2,3,5</sub> and D<sub>2,3,6</sub> described above, R<sub>7</sub> is preferably H or methyl, more preferably H.

For compounds of Formula I falling within any one of groups A, B, B<sub>2</sub>, B<sub>3</sub>, B<sub>4</sub>, C, C<sub>2,3</sub>,  
20 C<sub>2,4</sub>, C<sub>2,5</sub>, C<sub>2,6</sub>, C<sub>3,4</sub>, C<sub>3,5</sub>, D, D<sub>2,3,5</sub> and D<sub>2,3,6</sub> described above, R<sub>8</sub> is preferably H.

For compounds of Formula I falling within any one of groups A, B, B<sub>2</sub>, B<sub>3</sub>, B<sub>4</sub>, C, C<sub>2,3</sub>, C<sub>2,4</sub>, C<sub>2,5</sub>, C<sub>2,6</sub>, C<sub>3,4</sub>, C<sub>3,5</sub>, D, D<sub>2,3,5</sub> and D<sub>2,3,6</sub> described above, R<sub>9</sub> is preferably H or fluoro, more preferably H.

25

For compounds of Formula I falling within any one of groups A, B, B<sub>2</sub>, B<sub>3</sub>, B<sub>4</sub>, C, C<sub>2,3</sub>, C<sub>2,4</sub>, C<sub>2,5</sub>, C<sub>2,6</sub>, C<sub>3,4</sub>, C<sub>3,5</sub>, D, D<sub>2,3,5</sub> and D<sub>2,3,6</sub> described above, R<sub>10</sub> is preferably H or fluoro, more preferably H.

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For compounds of Formula I falling within any one of groups A, B, B2, B3, B4, C, C2,3, C2,4, C2,5, C2,6, C3,4, C3,5, D, D2,3,5 and D2,3,6 described above, R1 is preferably a C<sub>2</sub>-C<sub>10</sub>alkyl group optionally substituted with from 1 to 7 halogen substituents and/or with from 1 to 3 substituents each independently selected from hydroxy, cyano, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkylthio (optionally substituted with from 1 to 3 halogen atoms) and C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 3 halogen atoms). More preferably, R1 is a C<sub>2</sub>-C<sub>10</sub>alkyl group optionally substituted with from 1 to 7 halogen substituents and/or with from 1 to 3 substituents each independently selected from hydroxy, cyano and C<sub>1</sub>-C<sub>4</sub>alkoxy.

10

For compounds of Formula I falling within any one of groups A, B, B2, B3, B4, C, C2,3, C2,4, C2,5, C2,6, C3,4, C3,5, D, D2,3,5 and D2,3,6 described above, n is preferably 1, R7, R8, R9 and R10 are preferably H and R1 is preferably a C<sub>2</sub>-C<sub>10</sub>alkyl group optionally substituted with from 1 to 7 halogen substituents and/or with from 1 to 3 substituents each independently selected from hydroxy, cyano, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkylthio (optionally substituted with from 1 to 3 halogen atoms) and C<sub>1</sub>-C<sub>4</sub>alkoxy (optionally substituted with from 1 to 3 halogen atoms). More preferably, R1 is a C<sub>2</sub>-C<sub>10</sub>alkyl group optionally substituted with from 1 to 7 halogen substituents and/or with from 1 to 3 substituents each independently selected from hydroxy, cyano and C<sub>1</sub>-C<sub>4</sub>alkoxy.

20

Particularly preferred compounds of Formula I include:

N-(1-methylethyl)-N- {[2-(trifluoromethyl)phenyl]methyl} piperidin-4-amine,

N-(2-methylpropyl)-N- {[4-(methoxy)phenyl]methyl} piperidin-4-amine,

25 N-(2-methylpropyl)-N- {[4-(chloro)phenyl]methyl} piperidin-4-amine,

N-(2-methylpropyl)-N-(phenylmethyl) piperidin-4-amine,

N-(2-methylpropyl)-N- {[4-(methyl)phenyl]methyl} piperidin-4-amine,

N-(2-methylpropyl)-N- {[3,4-(dichloro)phenyl]methyl} piperidin-4-amine,

N-(2-methylpropyl)-N- {[2-(trifluoromethyl)phenyl]methyl} piperidin-4-amine,

- N-(cyclohexylmethyl)-N-(phenylmethyl)piperidin-4-amine,  
N-(cyclohexylmethyl)-N-{{4-(chloro)phenyl}methyl}piperidin-4-amine,  
N-(cyclohexylmethyl)-N-{{4-(methoxy)phenyl}methyl}piperidin-4-amine,  
N-(cyclohexylmethyl)-N-{{4-(methyl)phenyl}methyl}piperidin-4-amine,  
5 N-(cyclohexylmethyl)-N-{{3,4-(dichloro)phenyl}methyl}piperidin-4-amine,  
N-(cyclohexylmethyl)-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine,  
N-(cyclopropylmethyl)-N-{{4-(chloro)phenyl}methyl}piperidin-4-amine,  
N-(cyclopropylmethyl)-N-{{4-(methoxy)phenyl}methyl}piperidin-4-amine,  
N-(cyclopropylmethyl)-N-{{4-(methyl)phenyl}methyl}piperidin-4-amine,  
10 N-(cyclopropylmethyl)-N-{{3,4-(dichloro)phenyl}methyl}piperidin-4-amine,  
N-(cyclopropylmethyl)-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine,  
N-(butyl)-N-{{4-(chloro)phenyl}methyl}piperidin-4-amine,  
N-(butyl)-N-{{4-(methoxy)phenyl}methyl}piperidin-4-amine,  
N-(butyl)-N-{{4-(methyl)phenyl}methyl}piperidin-4-amine,  
15 N-(butyl)-N-{{3,4-(dichloro)phenyl}methyl}piperidin-4-amine,  
N-(butyl)-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine,  
N-(2-methylpropyl)-N-{{2-(cyano)phenyl}methyl}piperidin-4-amine,  
N-(2-methylpropyl)-N-{{4-(trifluoromethyl)phenyl}methyl}piperidin-4-amine,  
N-(2-methylpropyl)-N-{{3-(methyl)phenyl}methyl}piperidin-4-amine,  
20 N-(2-methylpropyl)-N-{{4-(phenyl)phenyl}methyl}piperidin-4-amine,  
N-(2-methylpropyl)-N-{{5-fluoro-2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine,  
N-(2-methylpropyl)-N-{{2,4-di-(trifluoromethyl)phenyl}methyl}piperidin-4-amine,  
N-(2-methylpropyl)-N-{{2-naphthyl}methyl}piperidin-4-amine,  
N-(2-methylpropyl)-N-{{2-(methylthio)phenyl}methyl}piperidin-4-amine,  
25 N-(2-methylpropyl)-N-{{1-naphthyl}methyl}piperidin-4-amine,  
N-(2-methylpropyl)-N-[(3-cyanophenyl)methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[(3,5-dichlorophenyl)methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[(2,4-dimethoxyphenyl)methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[(2,3-dichlorophenyl)methyl]piperidin-4-amine,  
30 N-(2-methylpropyl)-N-{{4-(methoxycarbonyl)phenyl}methyl}piperidin-4-amine,  
N-(2-methylpropyl)-N-[(2,4-difluorophenyl)methyl]piperidin-4-amine,

- N-(2-methylpropyl)-N-{{2-(trifluoromethoxy)phenyl}methyl}piperidin-4-amine,  
N-(2-methylpropyl)-N-[(2-fluorophenyl)methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[(2-chlorophenyl)methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[(2-methoxyphenyl)methyl]piperidin-4-amine,  
5 N-(2-methylpropyl)-N-[(2-methylphenyl)methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[(2-bromophenyl)methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[(3-fluorophenyl)methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[(3-chlorophenyl)methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[(3-methoxyphenyl)methyl]piperidin-4-amine,  
10 N-(2-methylpropyl)-N-{{3-(trifluoromethyl)phenyl}methyl}piperidin-4-amine,  
N-(2-methylpropyl)-N-{{3-(trifluoromethoxy)phenyl}methyl}piperidin-4-amine,  
N-(2-methylpropyl)-N-[(2,6-dichlorophenyl)methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[(4-methylthiophenyl)methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[(2,4-dimethylphenyl)methyl]piperidin-4-amine,  
15 N-ethyl-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine,  
N-propyl-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine,  
N-pentyl-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine,  
N-(3-methylbutyl)-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine,  
N-(3,3-dimethylbutyl)-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine,  
20 N-(2-ethylbutyl)-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine,  
N-(2-methylprop-2-enyl)-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine,  
N-(2-methylpropyl)-N-{{3-(trifluoromethylthio)phenyl}methyl}piperidin-4-amine,  
N-(2-methylpropyl)-N-{{2-(trifluoromethylthio)phenyl}methyl}piperidin-4-amine,  
N-(2-methylpropyl)-N-[(3-bromophenyl)methyl]piperidin-4-amine,  
25 N-(2-methylpropyl)-N-[(3-phenoxyphenyl)methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-{{3-(difluoromethoxy)phenyl}methyl}piperidin-4-amine,  
N-(2-methylpropyl)-N-[(2,5-dimethylphenyl)methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[(4-cyanophenyl)methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[(2-ethoxyphenyl)methyl]piperidin-4-amine,  
30 N-(2-methylpropyl)-N-[(4-fluorophenyl)methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[(3-ethoxyphenyl)methyl]piperidin-4-amine,



- N-(2-methylpropyl)-N-[(2-chloro-6-fluorophenyl)methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[(2-biphenyl)methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[(3-biphenyl)methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[[2-fluoro-6-(trifluoromethyl)phenyl]methyl]piperidin-4-amine,  
5 N-(2-methylpropyl)-N-[(3,5-difluorophenyl)methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[(3,5-dimethylphenyl)methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[(3,5-dimethoxyphenyl)methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[[3-fluoro-5-(trifluoromethyl)phenyl]methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[(5-fluoro-2-methoxyphenyl)methyl]piperidin-4-amine,  
10 N-(2-methylpropyl)-N-[[4-(trifluoromethoxy)phenyl]methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[[3-(methoxycarbonyl)phenyl]methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[(2,6-dimethylphenyl)methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[[2-(tert-butylthio)phenyl]methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[[4-fluoro-2-(trifluoromethyl)phenyl]methyl]piperidin-4-amine,  
15 N-(3,3-dimethylbutyl)-N-[(2-bromophenyl)methyl]piperidin-4-amine,  
N-(3,3-dimethylbutyl)-N-[(2-methylphenyl)methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[(2,4-dichlorophenyl)methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[[2-(difluoromethoxy)phenyl]methyl]piperidin-4-amine,  
N-(3,3-dimethylbutyl)-N-[[5-fluoro-2-(trifluoromethyl)phenyl]methyl]piperidin-4-amine,  
20 N-(3-ethylbutyl)-N-[(2-bromophenyl)methyl]piperidin-4-amine,  
N-(3-ethylbutyl)-N-[(2-methylphenyl)methyl]piperidin-4-amine,  
N-propyl-N-[(2-chlorophenyl)methyl]piperidin-4-amine,  
N-(3,3-dimethylbutyl)-N-[(2-phenoxyphenyl)methyl]piperidin-4-amine,  
N-(3-ethylbutyl)-N-[(2-chloro-6-fluorophenyl)methyl]piperidin-4-amine,  
25 N-(3,3-dimethylbutyl)-N-[(2-biphenyl)methyl]piperidin-4-amine,  
N-(2-methoxyethyl)-N-[[2-(trifluoromethyl)phenyl]methyl]piperidin-4-amine,  
N-(2-ethylbutyl)-N-[[5-fluoro-2-(trifluoromethyl)phenyl]methyl]piperidin-4-amine,  
N-cyclopentyl-N-[[2-(trifluoromethyl)phenyl]methyl]piperidin-4-amine,  
N-(3,3,3-trifluoropropyl)-N-[[2-(trifluoromethyl)phenyl]methyl]piperidin-4-amine,  
30 N-(4,4,4-trifluorobutyl)-N-[[2-(trifluoromethyl)phenyl]methyl]piperidin-4-amine,  
N-(2,2-dimethylpropyl)-N-[[2-(trifluoromethyl)phenyl]methyl]piperidin-4-amine,

- N-(2-methylpropyl)-N-{{2-(trifluoromethyl)phenyl}ethyl}piperidin-4-amine,  
N-(2-methylpropyl)-N-{{2-(methylsulphonyl)phenyl}methyl}piperidin-4-amine,  
N-(2-ethylbutyl)-N-[(2-biphenyl)methyl]piperidin-4-amine,  
N-(cyclohexylmethyl)-N-[(2-biphenyl)methyl]piperidin-4-amine,  
5 N-(2-ethylbutyl)-N-[(2-phenoxyphenyl)methyl]piperidin-4-amine,  
N-(2-methylpropyl)-N-[(2-phenoxyphenyl)methyl]piperidin-4-amine,  
N-(cyclohexylmethyl)-N-[(2-phenoxyphenyl)methyl]piperidin-4-amine,  
N-(2-ethylpropyl)-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine,  
N-butyl-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine,  
10 N-(cyclopropylmethyl)-N-[(2-biphenyl)methyl]piperidin-4-amine,  
N-(cyclopropylmethyl)-N-[(2-phenoxyphenyl)methyl]piperidin-4-amine,  
N-(2-methoxyethyl)-N-[(2-methylthio)methyl]piperidin-4-amine,  
N-(2-methoxyethyl)-N-{{2-(difluoromethoxy)phenyl}methyl}piperidin-4-amine,  
N-(2-methoxyethyl)-N-[(2-methyl)methyl]piperidin-4-amine,  
15 N-(2-methoxyethyl)-N-[(2-chlorophenyl)methyl]piperidin-4-amine,  
N-(2-methoxyethyl)-N-{{4-fluoro-2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine,  
N-(2-methoxyethyl)-N-[(2,4-dichlorophenyl)methyl]piperidin-4-amine,  
N-(cyclopropylmethyl)-N-[(2-methylthiophenyl)methyl]piperidin-4-amine,  
N-(cyclopropylmethyl)-N-[(2-methylphenyl)methyl]piperidin-4-amine,  
20 N-(cyclopropylmethyl)-N-[(2-chlorophenyl)methyl]piperidin-4-amine,  
N-(cyclopropylmethyl)-N-{{4-fluoro-2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine,  
N-(cyclopropylmethyl)-N-[(2,4-dichlorophenyl)methyl]piperidin-4-amine,  
N-(3-methylbutyl)-N-[(2-phenoxyphenyl)methyl]piperidin-4-amine,  
25 N-(3-methylbutyl)-N-[(2-biphenyl)methyl]piperidin-4-amine,  
N-(2,3-dimethylpropyl)-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine  
(racemate),  
N-(2,3-dimethylpropyl)-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine (R  
isomer),  
30 N-(2,3-dimethylpropyl)-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine (S  
isomer),

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- N-propyl-N-[(2-methylthiophenyl)methyl]piperidin-4-amine,  
N-propyl-N-[[2-(difluoromethoxy)phenyl]methyl]piperidin-4-amine,  
N-propyl-N-[(2-methylphenyl)methyl]piperidin-4-amine,  
N-propyl-N-[[4-fluoro-2-(trifluoromethyl)phenyl]methyl]piperidin-4-amine,  
5 N-propyl-N-[(2,4-dichlorophenyl)methyl]piperidin-4-amine,  
N-butyl-N-[(2-methylthiophenyl)methyl]piperidin-4-amine,  
N-butyl-N-[[2-(difluoromethoxy)phenyl]methyl]piperidin-4-amine,  
N-butyl-N-[(2-methylphenyl)methyl]piperidin-4-amine,  
N-butyl-N-[(2-chlorophenyl)methyl]piperidin-4-amine,  
10 N-butyl-N-[[4-fluoro-2-(trifluoromethyl)phenyl]methyl]piperidin-4-amine,  
N-butyl-N-[(2,4-dichlorophenyl)methyl]piperidin-4-amine,  
N-(2-Methylpropyl)-N-[(2,3,6-(trichloro)phenyl)methyl]piperidin-4-amine,  
N-(2-Methylpropyl)-N-[(2,3,5-(trichloro)phenyl)methyl]piperidin-4-amine,  
N-(2-Methylpropyl)-N-[[3-chloro-4-fluoro)phenyl]methyl]piperidin-4-amine,  
15 N-(2-Methylpropyl)-N-[[2-chloro-3-(trifluoromethyl)phenyl]methyl]piperidin-4-amine,  
N-(2-Methylpropyl)-N-[[2,5-dichloro)phenyl]methyl]piperidin-4-amine,  
N-(2-Methylpropyl)-N-[[3-chloro-2-fluoro-6-(trifluoromethyl))phenyl]methyl]piperidin-  
4-amine,  
N-(2-Methylpropyl)-N-[[3-chloro-2-fluoro-5-(trifluoromethyl))phenyl]methyl]piperidin-  
20 4-amine,  
N-(2-Methylpropyl)-N-[[3-chloro-2-fluoro)phenyl]methyl]piperidin-4-amine,  
N-(2-Methylpropyl)-N-[[4-chloro-3-(trifluoromethyl))phenyl]methyl]piperidin-4-amine,  
N-(2-Methylpropyl)-N-[[2-chloro-5-(trifluoromethyl))phenyl]methyl]piperidin-4-amine,  
N-(2-Methylpropyl)-N-[[2-chloro-6-fluoro-3-methylphenyl]methyl]piperidin-4-amine,  
25 N-(2-Methylpropyl)-N-[[6-chloro-2-fluoro-3-methylphenyl]methyl]piperidin-4-amine,  
N-(1-Propyl)-N-[[2,3-dichloro)phenyl]methyl]piperidin-4-amine,  
N-(1-Butyl)-N-[[2,3-dichloro)phenyl]methyl]piperidin-4-amine,  
N-(Cyclopropylmethyl)-N-[[2,3-dichloro)phenyl]methyl]piperidin-4-amine,  
N-(2,2-dimethylpropyl)-N-[[2,3-dichloro)phenyl]methyl]piperidin-4-amine,  
30 N-(2-Methylpropyl)-N-[[3-chloro-2-methyl)phenyl]methyl]piperidin-4-amine,  
N-(2-Methylpropyl)-N-[[2-chloro-3-methyl)phenyl]methyl]piperidin-4-amine,

- N-(2,2-Dimethylpropyl)-N-{{[1,1-biphenyl]-2-yl-methyl}piperidin-4-amine,  
N-(2,2-Dimethylpropyl)-N-{{(2-phenoxyphenyl)methyl}piperidin-4-amine,  
N-(2-Methylpropyl)-N-{{(2-chloro-4-fluoro)phenyl]methyl}piperidin-4-amine,  
N-(1-Propyl)-N-{{(2-chloro-4-fluoro)phenyl]methyl}piperidin-4-amine,  
5 N-(Cyclohexylmethyl)-N-{{(4-fluoro-2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine,  
N-(Cyclobutylmethyl)-N-{{(4-fluoro-2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine,  
N-(Cyclopentylmethyl)-N-{{(4-fluoro-2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine,  
10 amine,  
N-(Cycloheptylmethyl)-N-{{(4-fluoro-2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine,  
N-(Cyclobutylmethyl)-N-{{(2,4-dichloro-phenyl)]methyl}piperidin-4-amine,  
N-(2-Methylpropyl)-N-{{(2-fluoro-4-(trifluoromethyl))phenyl]methyl}piperidin-4-amine,  
15 N-{{(2-Trifluoromethyl)phenyl]methyl}-N-tetrahydro-2H-pyran-4-yl-piperidin-4-amine,  
N-(Cyclopentyl)-N-{{(2,3-dichloro)phenyl]methyl}piperidin-4-amine,  
N-(3,3,3-Trifluoropropyl)-N-{{(2,3-dichloro)phenyl]methyl}piperidin-4-amine,  
N-{{(2,3-dichloro)phenyl]methyl}-N-tetrahydro-2H-pyran-4-yl-piperidin-4-amine,  
N-(2-Methylpentyl)-N-{{(2,3 dichloro)phenyl]methyl}piperidin-4-amine,  
20 N-(2-Methylpropyl)-4-methyl-N-{{(2-(trifluoromethyl)phenyl]methyl}piperidin-4-amine,  
N-(2-Methylpropyl)-N-{{(3-chloro-2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine,  
N-(2-Hydroxyethyl)-N-{{(4-fluoro-2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine,  
N-(2,2,2-Trifluoroethyl)-N-{{(2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine,  
N-(2-Methylpropyl)-N-{{2-chloro-4-(methylsulfonyl)phenyl]methyl}-piperidin-4-amine,  
25 N-(3-Methoxypropyl)-N-{{(2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine,  
N-(3-Methoxypropyl)-N-{{(2,4-dichloro)phenyl]methyl}piperidin-4-amine,  
N-(3-Methoxypropyl)-N-{{(4-fluoro-2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine,  
amine,  
N-{2-[(1-Methylethyl)oxy]ethyl}}-N-{{(2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine,  
30 amine,  
N-{2-[(1-Methylethyl)oxy]ethyl}}-N-{{(2,4-dichloro)phenyl]methyl}piperidin-4-amine,

- N-{2-[(1-Methylethyl)oxy]ethyl}-N-{[(4-fluoro-2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine,  
 N-[2-(Ethyloxy)ethyl]-N-{[(2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine,  
 N-[2-(Ethyloxy)ethyl]-N-{[2,4-dichlorophenyl]methyl}piperidin-4-amine,  
 5 N-[2-(Ethyloxy)ethyl]-N-{[(4-fluoro-2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine,  
 N-{[(4-Fluoro-2-trifluoromethyl)phenyl]methyl}-N-(tetrahydro-2H-pyran-4-ylmethyl)-piperidin-4-amine,  
 N-[2-(Methylthio)ethyl]-N-{[(4-fluoro-2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine,  
 10 N-{[(2,3-Dichloro)phenyl]methyl}-N-tetrahydro-2H-pyran-4-yl-piperidin-4-amine,  
 N-{4-[(Methyl)oxy]butyl}-N-{[(2,4-dichloro)phenyl]methyl}piperidin-4-amine,  
 N-(3-hydroxy-3-methylbutyl)-N-{[(2,4-dichlorophenyl)methyl]piperidin-4-amine,  
 N-(2-hydroxy-2-methylpropyl)-N-{[(2,4-dichlorophenyl)methyl]piperidin-4-amine,  
 15 N-{2-[(Trifluoromethyl)oxy]ethyl}-N-{[(2,4-dichloro)phenyl]methyl}piperidin-4-amine,  
 N-{2-[(Trifluoromethyl)oxy]ethyl}-N-{[(4-fluoro-2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine,  
 N-{2-[(Trifluoromethyl)oxy]ethyl}-N-{[(2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine,  
 20 N-(Cyclopropylmethyl)-N-{[(4-fluoro-2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine,  
 2-Methylpropan-2-ol-1-[[4-fluoro-2-(trifluoromethyl)phenyl]methyl]piperidin-4-amine],  
 N-[1-(4-Fluoro-2-(trifluoromethyl)phenyl)ethyl]-N-(cyclopropylmethyl)piperidin-4-amine,  
 25 N-(3-Hydroxypropyl)-N-[[2,4-dichlorophenyl]methyl](piperidin-4-amine,  
 N-(2-Hydroxyethyl)-N-[[2,4-Dichlorophenyl]methyl](piperidin-4-amine],  
 3-[[4-Fluoro-2-(trifluoromethyl)phenyl]methyl](piperidin-4-yl)amino]propanenitrile,  
 3-[[4-Fluoro-2-(trifluoromethyl)phenyl]methyl](piperidin-4-yl)amino]butanenitrile,  
 N-(Cyclopropylmethyl)-N-{[(2,3-Dichloro)phenyl]methyl}piperidin-4-amine,  
 30 3-[[4-Fluoro-2-(trifluoromethyl)phenyl]methyl](piperidin-4-yl)amino]2,2-dimethylpropanenitrile,

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- 4-[[[(2,4-Dichlorophenyl)methyl](piperidin-4-yl)amino]-2,2-dimethylbutanenitrile,  
4-[[[(4-Fluoro-2-(trifluoromethyl))phenyl)methyl](piperidin-4-yl)amino]-2,2-  
dimethylbutanenitrile,  
3-[[[(2,4-Dichloro)phenyl)methyl](piperidin-4-yl)amino]-butanenitrile,  
5 3-[[[(2-(Trifluoromethyl)phenyl)methyl](piperidin-4-yl)amino]-butanenitrile,  
N-(3-Methyl-3-hydroxybutyl)-N-[[[4-fluoro-2-(trifluoromethyl)phenyl)methyl]piperidin-  
4-amine,  
1-[[[(2,4-Dichloro)phenyl)methyl](piperidin-4-yl)amino] cyclopentanol, and  
N-[1-Fluorocyclopropyl)methyl]-N-[[[(2,4-dichloro)phenyl)methyl]piperidin-4-amine.

10

- The present invention includes pharmaceutically acceptable salts of the compounds of  
formula I. Suitable salts include acid addition salts, including salts formed with inorganic  
acids (for example hydrochloric, hydrobromic, nitric, sulphuric or phosphoric acid) or  
with organic acids, such as organic carboxylic acids (for example fumaric, pyruvic,  
15 lactobionic, glycolic, oxalic, maleic, hydroxymaleic, malic, citric, salicylic, o-  
acetoxybenzoic or tartaric acid), or organic sulphonic acids (for example toluene-p-  
sulphonic, bisethanesulphonic or methanesulphonic acid).

- It will be appreciated that certain compounds of formula I may possess one or more chiral  
20 centres. Where a structural formula does not specify the stereochemistry at one or more  
chiral centres, it encompasses all possible stereoisomers and all possible mixtures of  
stereoisomers (including, but not limited to, racemic mixtures) which may result from  
stereoisomerism at each of the one or more chiral centers.

- 25 As mentioned above, the compounds of the present invention and their pharmaceutically  
acceptable salts inhibit the uptake of one or more of the monoamine neurotransmitters  
serotonin, dopamine and norepinephrine.

- In view of these properties, the compounds of the present invention and their  
30 pharmaceutically acceptable salts are indicated for use in treating disorders which are  
caused by or linked to decreased neurotransmission of one or more of these monoamines.

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Such disorders include disorders of the central and/or peripheral nervous system such as, for example, adjustment disorders (including depressed mood, anxiety, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and mood), age-associated learning and mental disorders (including Alzheimer's disease), alcohol  
5 addiction, antinociceptive pain, apathy, attention-deficit (or other cognitive) disorders due to general medical conditions, attention-deficit hyperactivity disorder (ADHD), autism, bipolar disorder, borderline personality disorder, brain trauma, cardiovascular disorders, chronic fatigue syndrome, chronic or acute stress, Chron's disease, cognitive disorders including mild cognitive impairment (MCI), conduct disorder, cyclothymic disorder,  
10 dementia of ageing, dementia of the Alzheimers type (DAT), depression (including adolescent depression and minor depression), dyspepsia, disruptive behavior disorders, drug addiction including cocaine abuse, dysthymic disorder, eating disorders (including bulimia and anorexia nervosa), emesis, emotional dysregulation, epilepsy, fibromyalgia and other somatoform disorders (including somatization disorder, conversion disorder,  
15 pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated somatoform disorder, and somatoform NOS), functional bowel disorders, gastric motility disorders, gastroesophageal reflux for functional bowel disorders, gastrointestinal disorders, generalized anxiety disorder (GAD), headache, hot flushes/flushes, hypertension, hypotensive states including orthostatic hypotension, ileitis, impulsive control disorders,  
20 incontinence (i.e., stress incontinence, genuine stress incontinence, urge incontinence and mixed incontinence), inflammatory bowel disorders, inhalation disorders, interstitial cystitis, intoxication disorders (alcohol addiction), irritable bowel syndrome, ischemic bowel disease, mania, memory loss, mutism, nicotine addiction, obesity (i.e., reducing the weight of obese or overweight patients), obsessive compulsive disorders and related  
25 spectrum disorders, oppositional defiant disorder, pain (including chronic pain, inflammatory pain, neuropathic pain, non-neuropathic non-inflammatory pain, persistent pain, persistent pain of inflammatory and/or neuropathic origin, headache and migraine), panic disorders, Parkinsonism, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder (i.e., premenstrual syndrome and late luteal phase  
30 dysphoric disorder), psoriasis, psychoactive substance use disorders, psychotic disorders (including schizophrenia, schizoaffective and schizophreniform disorders), seasonal

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affective disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome (i.e., wherein a patient who fails to maintain a satisfactory response to SSRI therapy after an initial period of satisfactory response), senile dementia, sexual dysfunction (including premature ejaculation and erectile difficulty), sleep disorders (such as narcolepsy and enuresis), smoking cessation, social phobia (including social anxiety disorder), specific developmental disorders, substance abuse (including alcohol addiction, tobacco abuse, symptoms caused by withdrawal or partial withdrawal from the use of tobacco or nicotine and drug addiction including cocaine abuse), TIC disorders (e.g., Tourette's Disease), tobacco addiction, trichotilomania, ulcerative colitis, urethral syndrome, vascular dementia and cognitive impairment associated with schizophrenia (CIAS).

One preferred group of compounds of the present invention selectively inhibit the reuptake of serotonin and norepinephrine over dopamine. Preferably said group of compounds of the present invention selectively inhibit the serotonin and norepinephrine transporters relative to the dopamine transporter by a factor of at least five, and even more preferably by a factor of at least ten. Compounds of the present invention with this pharmacological profile are particularly useful for the treatment of depression, eating disorders (including bulimia and anorexia nervosa), inflammatory bowel disorders, functional bowel disorders, dyspepsia, Chron's disease, ileitis, ischemic bowel disease, ulcerative colitis, gastroesophageal reflux for functional bowel disorders, irritable bowel syndrome, obesity, interstitial cystitis, urethral syndrome, gastric motility disorders, substance abuse (including alcoholism, tobacco abuse, symptoms caused by withdrawal or partial withdrawal from the use of tobacco or nicotine and drug addiction including cocaine abuse), pain (including inflammatory pain, neuropathic pain, non-neuropathic non-inflammatory pain, persistent pain, persistent pain of inflammatory and/or neuropathic origin, headache and migraine), incontinence (including stress urinary incontinence and urge incontinence), dementia of ageing, senile dementia, Alzheimer's, memory loss, Parkinsonism, attention-deficit disorder (including attention-deficit hyperactivity disorder), anxiety, social phobia, disruptive behavior disorders, impulsive control disorders, borderline personality disorder, chronic fatigue syndrome, panic disorders, obsessive compulsive disorder, post-traumatic stress disorder, schizophrenia,



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gastrointestinal disorders, cardiovascular disorders, hot flushes/flushes, emesis, sleep disorders, cognitive disorders, psychotic disorders, brain trauma, premenstrual syndrome or late luteal syndrome, sexual dysfunction (including premature ejaculation and erectile difficulty), autism, mutism and trichotilomania. They are more particularly useful for the treatment of depression, incontinence (particularly stress urinary incontinence) and pain (particularly persistent pain). They are most particularly useful for the treatment of persistent pain.

For clinical purposes, pain may be divided into two categories: acute pain and persistent pain. Acute pain is provoked by noxious stimulation produced by injury and/or disease of skin, deep somatic structures or viscera, or abnormal function of muscle or viscera that does not produce actual tissue damage. On the other hand, persistent pain can be defined as pain that persists beyond the usual course of an acute disease or a reasonable time for an injury to heal or that is associated with a chronic pathologic process that causes continuous pain or the pain recurs at intervals for months or years. If pain is still present after a cure should have been achieved, it is considered persistent pain. For the purpose of the present invention, persistent pain can be chronic non-remitting or recurrent. The difference in definition between acute and persistent pain is not merely semantic but has an important clinical relevance. For example, a simple fracture of the wrist usually remains painful for a week to 10 days. If the pain is still present beyond the typical course of treatment, it is likely that the patient is developing reflex sympathetic dystrophy, a persistent pain syndrome that requires immediate effective therapy. Early and effective intervention potentially prevents the undue disability and suffering, and avoids the potential development of a condition that becomes refractory to therapy.

Acute and persistent pain differ in etiology, mechanisms, pathophysiology, symptomatology, diagnosis, therapy, and physiological responses. In contrast to the transitory nature of acute pain, persistent pain is caused by chronic pathologic processes in somatic structures or viscera, by prolonged and sometimes permanent dysfunction of the peripheral or central nervous system, or both. Also, persistent pain can sometimes be attributed to psychologic mechanisms and/or environmental factors.

More specifically, persistent pain can be segmented into neuropathic pain (e.g. diabetic neuropathy, infectious neuropathic pain associated with AIDS, non-surgical carpal tunnel syndromes, post-herpetic neuralgia, cervical, thoracic and lumbosacral radiculopathies, stroke-related central pains, trigeminal neuralgia and complex regional pain syndromes I and II), inflammatory pain (e.g. polymyalgia, rheumatoid arthritis and osteoarthritis), and non-neuropathic non-inflammatory pain, non-neuropathic non-inflammatory chronic pain (NNNICP) (e.g. chronic fatigue syndrome, chronic back pain without radiculopathy, fibromyalgia, chronic tension type headaches, inflammatory bowel disorders, irritable bowel syndrome, whiplash injuries, chronic pelvic pain, TMJD and failed back).

Current therapies for persistent pain include opiates, barbiturate-like drugs such as thiopental sodium and surgical procedures such as neurectomy, rhizotomy, cordotomy, and corpectomy.

Another preferred group of compounds of the present invention selectively inhibit the reuptake of norepinephrine over serotonin and dopamine. Preferably said group of compounds of the present invention selectively inhibit the norepinephrine transporter relative to the serotonin and dopamine transporters by a factor of at least five, and even more preferably by a factor of at least ten. Compounds of the present invention with this pharmacological profile are particularly useful for the treatment of adjustment disorders (including depressed mood, anxiety, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and mood), age-associated learning and mental disorders (including Alzheimer's disease), alcohol addiction, anorexia nervosa, antinociceptive pain, apathy, attention-deficit (or other cognitive) disorders due to general medical conditions, attention-deficit hyperactivity disorder (ADHD), bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, cognitive disorders including mild cognitive impairment (MCI), conduct disorder, cyclothymic disorder, dementia of the Alzheimers type (DAT), depression (including adolescent depression and minor depression), dysthymic disorder, emotional dysregulation, fibromyalgia and other somatoform disorders (including somatization disorder, conversion disorder, pain

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disorder, hypochondriasis, body dysmorphic disorder, undifferentiated somatoform disorder, and somatoform NOS), generalized anxiety disorder (GAD), hypotensive states including orthostatic hypotension, incontinence (i.e., stress incontinence, genuine stress incontinence, and mixed incontinence), inhalation disorders, intoxication disorders (alcohol addiction), mania, migraine headaches, neuropathic pain, nicotine addiction, obesity (i.e., reducing the weight of obese or overweight patients), obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, pain including chronic pain, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder (i.e., premenstrual syndrome and late luteal phase dysphoric disorder), psoriasis, psychoactive substance use disorders, psychotic disorders (including schizophrenia, schizoaffective and schizophreniform disorders), seasonal affective disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome (i.e., wherein a patient who fails to maintain a satisfactory response to SSRI therapy after an initial period of satisfactory response), sleep disorders (such as narcolepsy and enuresis), social phobia (including social anxiety disorder), somatoform disorders, specific developmental disorders, TIC disorders (e.g., Tourette's Disease), tobacco addiction, vascular dementia and cognitive impairment associated with schizophrenia (CIAS). They are most particularly useful for the treatment of ADHD and schizophrenia.

Another preferred group of compounds of the present invention inhibit the reuptake of norepinephrine, serotonin and dopamine. Compounds of the present invention with this pharmacological profile are particularly useful for the treatment of a variety of conditions such as depression, obesity, compulsive disorders (including bulimia, obsessive compulsive disorder, drug addiction including cocaine abuse and alcohol addiction), hypertension, senile dementia, Alzheimer's, memory loss, attention-deficit hyperactivity disorder (ADHD), sexual dysfunction, Parkinsonism, anxiety, chronic fatigue syndrome, panic disorders, cognitive disorders, schizophrenia, gastrointestinal disorders, headache, cardiovascular disorders, epilepsy, smoking cessation, pain including chronic pain, urinary incontinence, emesis and sleep disorders. They are most particularly useful for the treatment of depression, chronic pain, smoking cessation and obesity.

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Accordingly, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof for use in therapy. In particular, the present invention provides a compound of Formula I or a pharmaceutically acceptable salt thereof for use as an inhibitor of the uptake of one or more of the monoamine neurotransmitters serotonin, dopamine and norepinephrine.

In another embodiment, the present invention provides a method for inhibiting the uptake of one or more monoamines selected from serotonin, dopamine and norepinephrine in a mammal, comprising administering to a mammal in need of such inhibition an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof. In particular, the present invention provides a method for treating a disorder which is caused by or linked to decreased neurotransmission of one or more monoamines selected from serotonin, dopamine and norepinephrine in a mammal, comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof. Such disorders include, for example, disorders of the central and/or peripheral nervous system.

In the context of the present specification the terms "treating" and "treatment" include prophylactic treatment as well as curative treatment.

In another alternative embodiment, the present invention provides for the use of a compound of Formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inhibiting the uptake of one or more monoamines selected from serotonin, dopamine and norepinephrine. In particular, the present invention provides for the use of a compound of Formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of a disorder which is caused by or linked to decreased neurotransmission of one or more monoamines selected from serotonin, dopamine and norepinephrine. Such disorders include, for example, disorders of the central and/or peripheral nervous system.

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The compounds may be administered by various routes and are usually employed in the form of a pharmaceutical composition.

Accordingly, in a further embodiment, the present invention provides a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable diluent or carrier.

Such compositions may be prepared by methods well known in the pharmaceutical art and normally comprise at least one active compound in association with a pharmaceutically acceptable diluent or carrier. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier or diluted by a carrier, and/or enclosed within a carrier which may, for example, be in the form of a capsule, sachet, paper or other container.

The compositions indicated can be sterilized and/or can contain auxiliaries such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for affecting the osmotic pressure, buffer substances, colourants, flavourings and/or one or more further active compounds. Compositions of the invention may be formulated so as to provide, quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 500 mg of the active ingredient.

In the context of the present specification, the term "unit dosage form" refers to physically discrete units suitable as unitary doses for human subjects and other mammals, each unit containing a predetermined quantity of one or more compounds of Formula I or pharmaceutically acceptable salts thereof, calculated to produce the desired therapeutic effect, together with a pharmaceutically acceptable diluent or carrier.

Compounds of formula I may be prepared by conventional organic chemistry techniques

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and also by solid phase synthesis.

In the present specification the abbreviation "boc" or "BOC" refers to the N-protecting group t-butyloxycarbonyl.

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In the present specification the abbreviation "TFA" refers to trifluoroacetic acid.

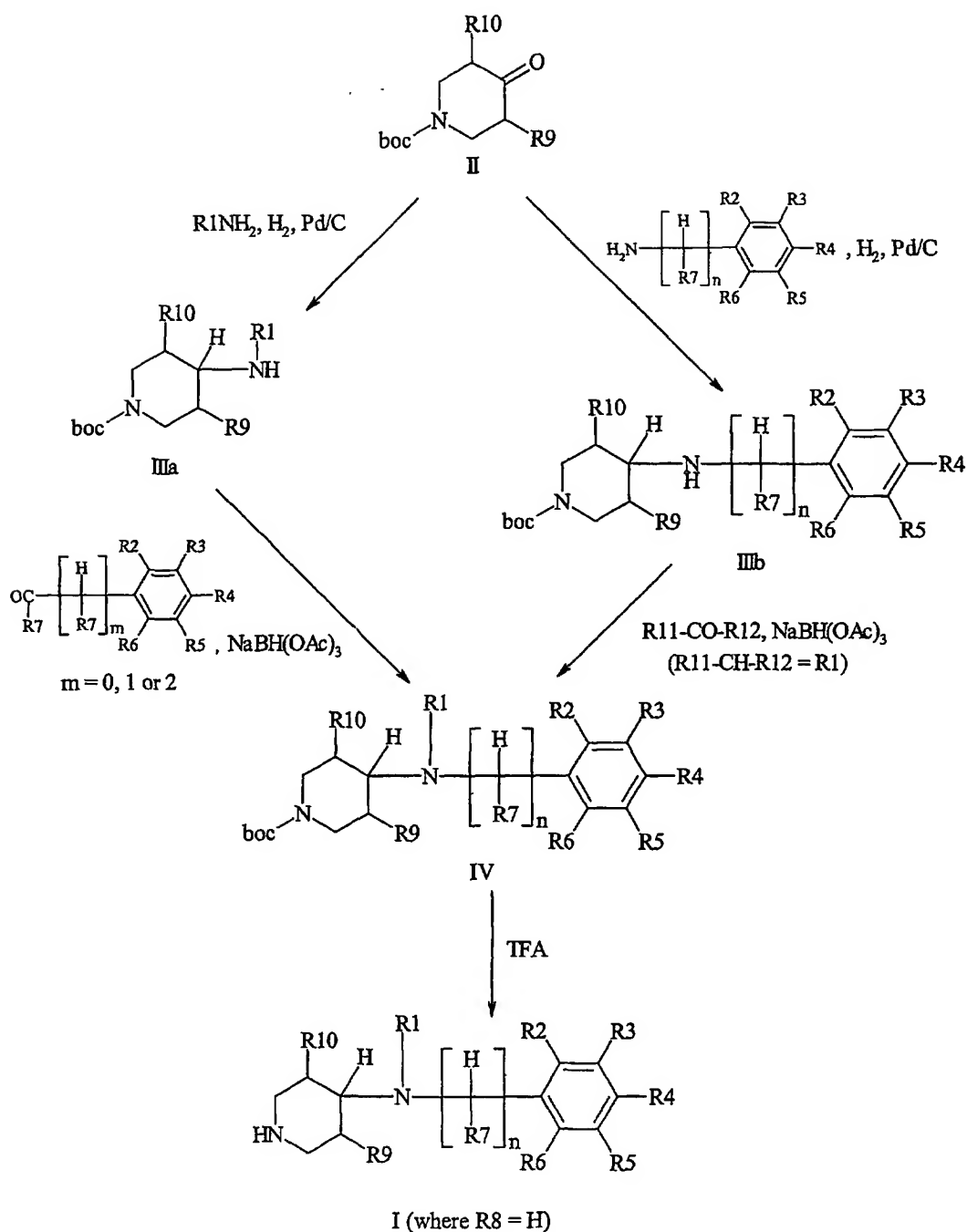
In the present specification the abbreviation "DMF" refers to dimethylformamide.

10 In the present specification the abbreviation "SPE" refers to solid phase extraction.

In the present specification the abbreviation "ACE-Cl" refers to  $\alpha$ -chloroethyl chloroformate.

15 When R8 is H, a suitable three-step conventional synthesis is outlined in the scheme shown below.

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A Boc-protected 4-piperidone (II) is reductively aminated with an amine to provide a 4-amino-piperidine (IIIa or IIIb). A second reductive amination with an aldehyde or ketone provides a Boc-protected compound of formula I (IV). The Boc group is removed under

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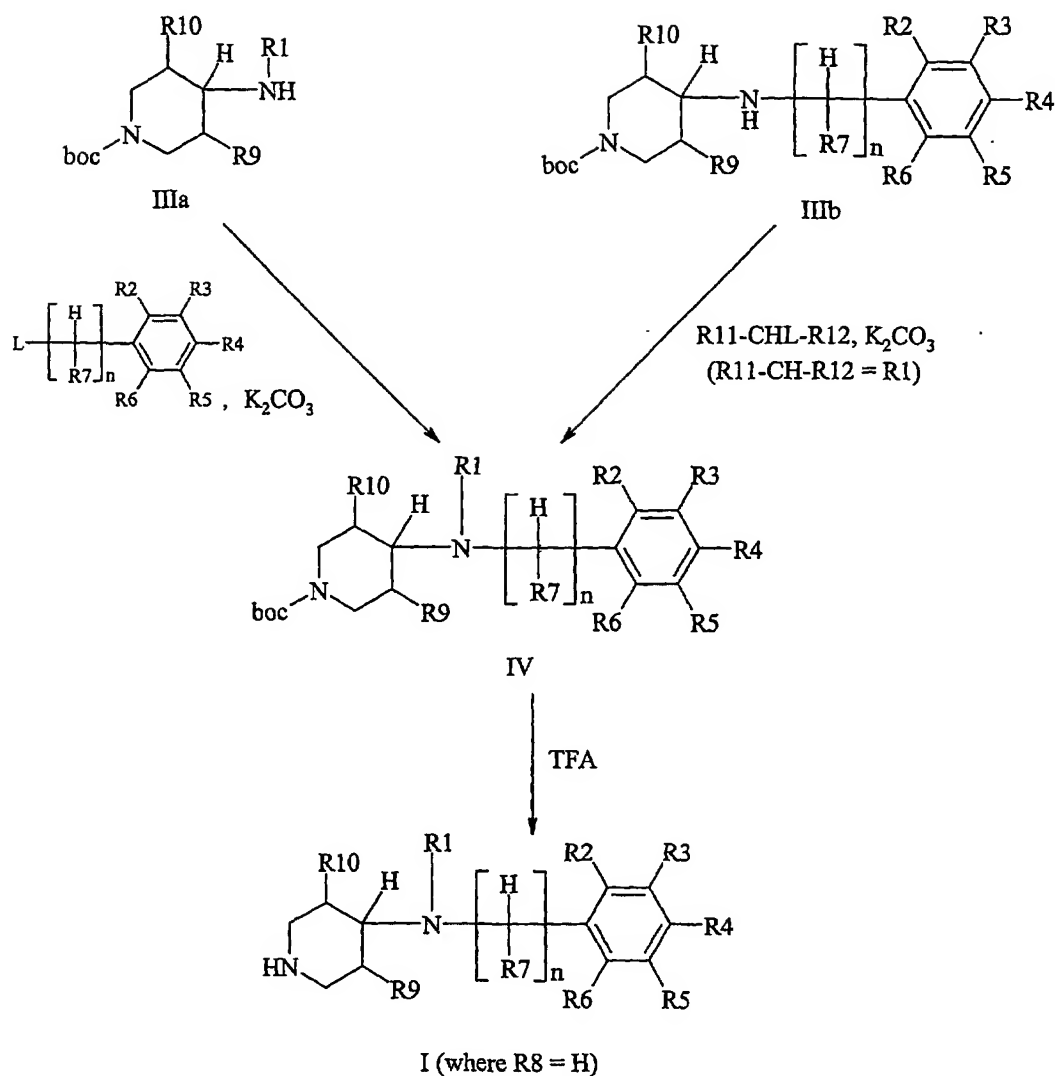
acidic conditions to provide a compound of formula I (where R8 is H). If desired, the compound of formula I (where R8 is H) may be converted to a suitable salt by addition of a suitable quantity of a suitable acid. In the schemes above (and below) R1 to R7, R9, R10 and n are as previously defined, m is 0, 1 or 2 and R11 and R12 are chosen such that  
5 R11-CH-R12 = R1.

Although the boc N-protecting group is used in the above illustration, it will be appreciated that other N-protecting groups (for example acetyl, benzyl or benzyloxycarbonyl) could also be used together with a deprotection step appropriate for the  
10 N-protecting group used. Similarly, other reducing agents (for example NaBH<sub>4</sub> or LiAlH<sub>4</sub>) may be used in the reductive amination steps and other acids (for example HCl) may be used in the deprotection step.

As an alternative to the second reductive amination step, compound IIIa or IIIb may be  
15 subjected to an alkylation step as shown below (L represents a suitable leaving group – for example Br or tosyl).



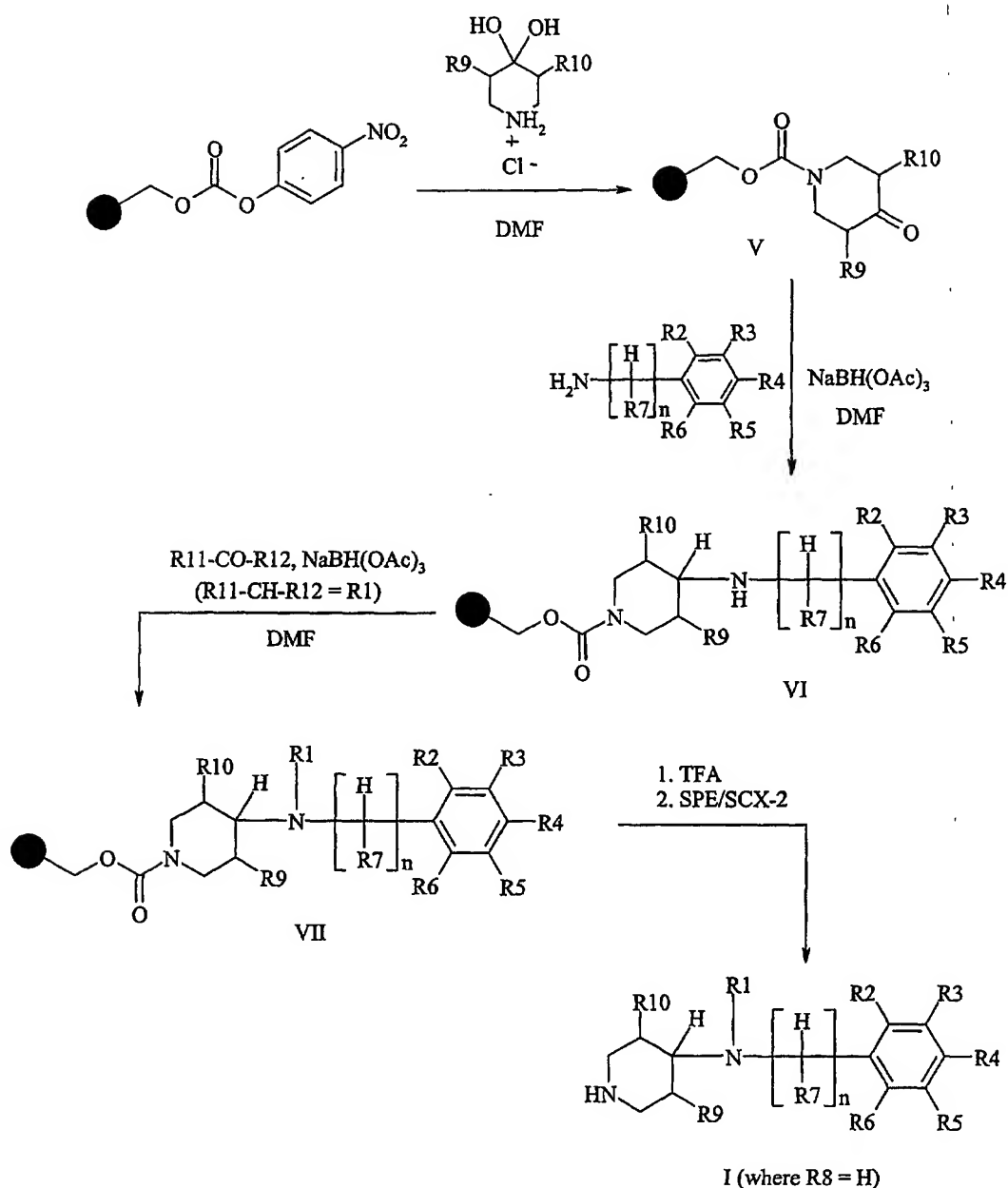
-41-



Once again, N-protection other than boc may also be used together with a suitable deprotection step. Similarly, bases other than potassium carbonate (e.g NaH) may be used  
 5 for the alkylation step

Using essentially the same chemical reactions as in the first scheme above, the compounds of formula I (where R8 is H) may also be prepared by a solid phase parallel synthesis technique as outlined in the scheme shown below.

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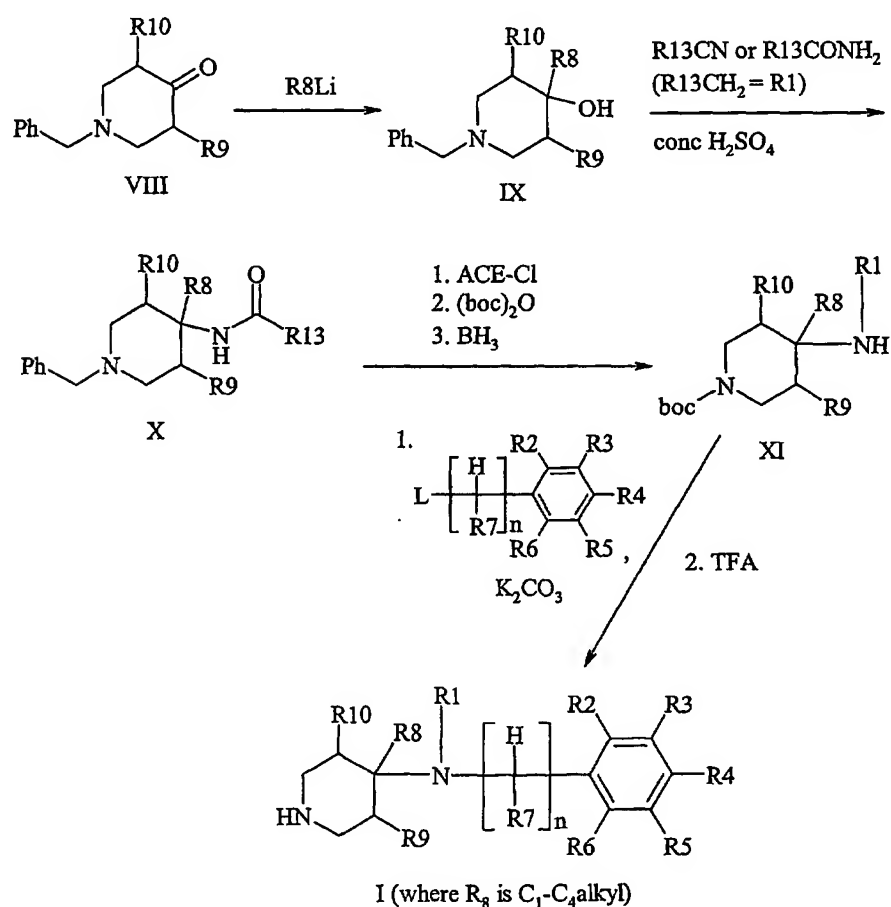
A piperidone hydrate is attached to a polystyrene resin to provide a resin bound piperidone (V). Aliquots are reductively aminated to provide a resin bound secondary amine (VI) that can undergo a further reductive amination with an aldehyde or ketone to give the tertiary amine (VII). Acidic cleavage from the resin and SPE provides

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compounds of formula I (where R<sub>8</sub> is H) which may be purified using, for example, the SCX-2 derivatised silica.

Although NaBH(OAc)<sub>3</sub> is used in the above illustration, it will be appreciated that other reducing agents (for example NaBH<sub>4</sub> or LiAlH<sub>4</sub>) may be used in the reductive amination steps and other acids (for example HCl) may be used in the deprotection step. Solid phase resins other than the p-nitrophenylcarbonate-polystyrene resin illustrated above may also be employed.

10 When R<sub>8</sub> is C<sub>1</sub>-C<sub>4</sub>alkyl, a conventional synthetic route is outlined in the scheme shown below.

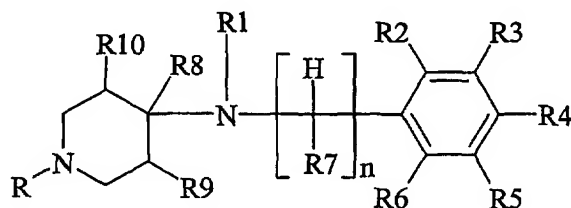


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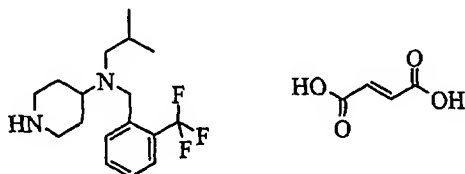
A benzyl-protected 4-piperidone (VIII) is alkylated with an alkyllithium reagent to provide a 4-amino-piperidinol (IX). Treatment with an alkylnitrile or alkylamide under strongly acidic conditions provides a secondary amide (X) which may be deprotected, boc-protected and reduced to provide a secondary amine (XI). Alkylation of the secondary amine (XI) followed by removal of the boc group provides a compound of formula I (where R8 is C<sub>1</sub>-C<sub>4</sub>alkyl). In the scheme above L is a leaving group as previously defined and R13 is chosen such that R13-CH<sub>2</sub> = R1.

Although the benzyl and boc N-protecting groups are used in the above illustration, it will be appreciated that other N-protecting groups could also be used in their place together with deprotection steps appropriate for those N-protecting groups. Similarly, other reducing agents may be used in the amidecarbonyl reduction step and other organometallics or bases may be used in the respective alkylation steps.

The present invention also provides a process for producing a compound of formula I above, which comprises deprotecting a compound of the formula



where R is an N-protecting group. Suitable N-protecting groups will be known to the person skilled in the art and include, for example, boc, benzyl, benzyloxycarbonyl and acetyl.

**EXAMPLE 1:****N-(2-methylpropyl)-N-([2-(trifluoromethyl)phenyl]methyl)piperidin-4-amine fumarate****Method 1**

- 5 (i) N-BOC-piperidone (1.25g, 6.27mmol) and 2-trifluoromethylbenzylamine (1.1g, 6.28mmol) were hydrogenated at 60 psi in ethanol (30ml) in the presence of 5% palladium on charcoal (0.3g) using a Parr hydrogenator. After 2.5h, the catalyst was filtered off and the filtrate was evaporated to give an oil (2.5g). The oil was purified by flash chromatography over silica, ramping the solvent mixture from 20% cyclohexane in ethyl acetate to ethyl acetate to give 1,1-dimethylethyl 4-([2-(trifluoromethyl)phenyl]methyl)amino)piperidine-1-carboxylate as an oil (1.8g, 80%).  $\delta_H$  (300 MHz,  $CDCl_3$ ) 7.62-7.66 (2H, dd, 2 ArH), 7.50-7.55 (1H, t, ArH), 7.32-7.37 (1H, t, ArH), 3.97 (2H, s, ArCH<sub>2</sub>), 3.97-4.19 (2H, m, NCH<sub>2</sub>), 2.78-2.86 (2H, brt, NCH<sub>2</sub>), 2.64-2.74 (1H, m, NCH), 1.85-1.90 (2H, dd, CCH<sub>2</sub>), 1.50-1.24 (2H, m, CCH<sub>2</sub>), 1.46 (9H, s, 3x CCH<sub>3</sub>); LCMS 6min gradient method,  $R_t = 5.28$  min ( $M^+ + H$ ) = 415.
- 15 (ii) Sodium triacetoxyborohydride (0.497g, 2.35mmol) was added in two lots over 15min to a stirred mixture of 1,1-dimethylethyl 4-([2-(trifluoromethyl)phenyl]methyl)amino)piperidine-1-carboxylate (0.6g, 1.68mmol), isobutyraldehyde (0.483g, 6.70mmol), acetic acid (1.01g, 16.7mmol) and 1,2-dichloroethane (10ml). After stirring for 3 days under nitrogen, excess 5M sodium hydroxide was added and the mixture was stirred for 30 min. The mixture was extracted 3 times with dichloromethane. The dichloromethane extracts were combined, washed (H<sub>2</sub>O), dried (MgSO<sub>4</sub>) and evaporated to give an oil (0.7g). The oil was dissolved in ethanol (10ml) and 2M HCl in ether (3.5ml) was added and the mixture was stirred at
- 20 room temperature under nitrogen for 1 day. The solution was evaporated in vacuo at 50°C and the resulting oil was converted to the free base using a SCX-2 ion exchange column, eluting with methanol and then a 2.3M solution of ammonia in methanol to give an oil.

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The oil was converted to the fumarate salt (ethanol/ether) give the title product as a white solid (0.151g, 21%).  $\delta$  (300 MHz, MeOD) 7.95-7.98 (1H, d), 7.58-7.67 (2H, m), 7.38-7.43 (1H, t), 6.69 (2H, s), 3.87 (2H, s), 3.43-3.47 (2H, d), 2.77-2.97 (3H, m), 3.32-3.35 (2H, d), 2.02-2.06 (2H, m), 2.02-2.06 (3H, m), 0.90-0.92 (6H, d); LCMS 12 min gradient method, Rt = 5.6 min, ( $M^+ + H$ ) = 315.

## Method 2

(i) To a mixture of N-BOC-piperidone (22g, 110mmol) and 2-trifluoromethylbenzylamine (19.3g, 110mmol) in a Parr bottle was placed ethanol (300ml). Palladium on carbon (5%, 6g) was then added and the mixture hydrogenated at 65psi for 3hr. Reaction filtered through Celite, concentrated in vacuo to give 1,1-dimethylethyl 4-([2-(trifluoromethyl)phenyl]methyl)amino)piperidine-1-carboxylate as an oil (37.2g, 94%). LCMS- 6 mins gradient Rt = 2.69 ( $M^+ + 1$ ) 359.2 1H NMR ( $CDCl_3$ )  $\delta$  = 7.65-7.60 (2H, m), 7.55-7.50 (1H, m), 7.46-7.33 (1H, m), 4.10-3.95 (4H, m), 2.90-2.75 (2H, m), 2.70-2.61 (1H, m), 1.91-1.85 (2H, m), 1.49 (9H, s), 1.38-1.22 (2H, m).

(ii) A solution of 1,1-dimethylethyl 4-([2-(trifluoromethyl)phenyl]methyl)amino)piperidine-1-carboxylate (28.0g, 80.7mmol), isobutylaldehyde (23.27g, 29.4ml, 322.8mmol) and acetic acid (807mmol, 48.46g, 46.2ml) in 1,2-dichloroethane (500ml) at room temperature under nitrogen was stirred for 30min. Then sodium triacetoxyborohydride (112.9mmol, 23.9g) was added portion wise over 15min and the reaction left to stir at room temperature for 16h. Excess 2M NaOH was added to the reaction mixture until pH>12. The mixture was extracted into dichloromethane (3x 400ml). The combined organics were dried ( $MgSO_4$ ), filtered, and concentrated in vacuo to give the crude product as an oil. Purified using a silica column eluting with 0-5% ethyl acetate in cyclohexane: to yield an oil in two batches (12g and 10g each).

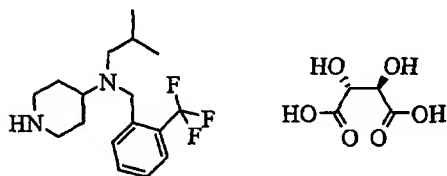
(iii) To a solution of the above oil (11.9g, 28.7mmol) in ethanol was placed HCl (conc. 28ml) and stirred at room temperature for 5days. An additional 50ml of HCl added and stirred for an additional 16h. Solvent removed in vacuo and then the crude was partitioned between dichloromethane/water and 2M NaOH added until pH>10. The phases were then separated, aqueous washed with dichloromethane and combined organics dried, ( $MgSO_4$ ), filtered and concentrated in vacuo to give a crude oil (7.5g,

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83%). Compound was purified on silica column DCM:MeOH:NH<sub>3</sub> (100:5:1) to give a N-(2-methylpropyl)-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine (4.5g, 50%). Crude fractions were then combined with the column fractions of a second similar reaction to give a total yield of (11.3g, 68%). The fumarate salt was made by taking the  
5 free base in ethanol (150ml) and whilst heating adding fumaric acid (1 equivalent) as an ethanol solution. The salt was washed with diethyl ether to yield the title product as a white solid (12.6g, 81% for salt formation).

**EXAMPLE 2:**

10 **N-(2-methylpropyl)-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine L-tartrate**



(i) To a solution of N-BOC-piperidin-4-one (500g, 2.5 mol) in 2.3L absolute ethanol, was added at room temperature isobutylamine (187.5g, 2.56 mol). After 30min stirring reaction mixture was transferred to a stainless steel hydrogenator and 40g anhydrous 10%  
15 Pd/C was added. Reactor was carefully purged with nitrogen and pressurised with hydrogen to 15psi over atmospheric pressure. Exothermic reaction immediately took place, temperature was not allowed to exceed 27°C. After 30min hydrogen was no longer consumed. Pressure was then increased to 22psi for a 15min period in order to assure reaction completion. Residual hydrogen pressure was released and reactor purged with  
20 nitrogen. Reaction mixture was then filtered on celite and solvent stripped out under vacuum up to 50°C. The product 4-isobutylamino-piperidine-1-carboxylic acid tert-butyl ester was isolated as pale yellow oil, 631g (98% yield). <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ ppm: 0.92 (d, J=6.57 Hz, 6 H), 1.27 (m, 2H), 1.46 (s, 9H), 1.72 (m, 1H), 1.84 (d, J=12.13 Hz, 2H), 2.45 (d, J=6.82 Hz, 2H), 2.58 (t, J=10.11 Hz, 1H), 2.81 (t, J=11.87 Hz, 2H), 4.03  
25 (m, 2H). <sup>13</sup>C NMR (250 MHz, CDCl<sub>3</sub>) δ ppm: 21.04, 28.85, 28.98, 33.02, 42.97, 55.28, 55.34, 79.61, 155.09.

(ii) To a solution of 4-isobutylamino-piperidine-1-carboxylic acid tert-butyl ester (20g,

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0.078 mol) in 200 ml anhydrous THF was added 2-trifluoromethylbenzaldehyde (16.37g, 0.094 mol) and then sodium triacetoxyborohydride (24.8g, 0.117 mol) in one portion. Very slight exothermic reaction was observed (temperature increased from 23 to 27°C). After 17h reaction at room temperature an additional portion of 2-  
5 trifluoromethylbenzaldehyde (3.3g, 0.019 mol) and then sodium triacetoxyborohydride (5g, 0.023 mol) was added. After 7h at room temperature no more N-BOC-4-isobutylaminopiperidine was detected.

Reaction mixture was cooled down to 0°C and a 1M NaOH solution 200 ml was added. The mixture was extracted twice with 200ml methyl tert-butyl ether, organic layers were  
10 isolated then dried over MgSO<sub>4</sub>, filtered, and collected liquors were concentrated under vacuum. The crude compound was then chromatographed on silica gel (eluant: heptane/ethyl acetate 95/5) to give 26.3g of pure compound 4-[isobutyl-(2-trifluoromethyl-benzyl)amino]piperidine-1-carboxylic acid tert-butyl ester (81% yield). As an alternative to chromatography the crude 4-[isobutyl-(2-trifluoromethyl-  
15 benzyl)amino]piperidine-1-carboxylic acid tert-butyl ester (10g) was dissolved in MeOH (34ml) at 40°C and water (8.5ml) was added dropwise under stirring. After cooling to 20°C, the white solid was filtered, washed 3 times with 3ml of 80:20 (v:v) MeOH/water and dried at 50°C under vacuum overnight (88% yield). <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ ppm 0.72 (d, J=6.61 Hz, 6 H), 1.28 (m, 11 H), 1.46 (m, 1 H), 1.57 (d, J=13.53 Hz, 2 H),  
20 2.10 (d, J=6.92 Hz, 2 H), 2.37 (m, 3 H), 3.64 (s, 2 H), 3.99 (d, J=12.59 Hz, 2 H), 7.13 (m, 1 H), 7.35 (t, J=7.55 Hz, 1 H), 7.43 (d, J=7.87 Hz, 1 H), 7.78 (d, J=7.87 Hz, 1 H). <sup>13</sup>C NMR (250 MHz, CDCl<sub>3</sub>) δ ppm: 21.17, 27.3, 28.12, 28.84, 44.17, 51.36, 58.43, 19.07, 79.73, 122.81, 125.74-125.84, 126.66, 127.17-128.17-128.64 (CF<sub>3</sub>), 130.24, 132.04, 140.94, 155.11.

25 (iii) To a mixture of 36 ml ethanol and 37%HCl 16 ml heated up to 50°C was added portion-wise 4-[isobutyl-(2-trifluoromethyl-benzyl)amino]piperidine-1-carboxylic acid tert-butyl ester (8 g, 0.01936 mol) gas evolution was observed. Reaction mixture was then heated to 60°C. After 30min reaction was completed.

The crude hydrochloride salt (8.4 g material) was then isolated by concentration of the  
30 reaction mixture under vacuum up to 50°C. This was neutralised by 100ml 1M NaOH solution, then extracted twice with 100ml methyl tert-butyl ether. Upper organic layer



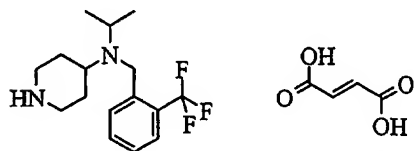
-49-

was then isolated, washed twice with 10ml 10% NaCl, dried over MgSO<sub>4</sub>. N-(2-methylpropyl)-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine 6.3 g was then isolated as pale yellow oil by filtration of the salts and evaporation of the solvent under vacuum up to 50°C. <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ ppm 0.89 (d, J=6.61 Hz, 6 H), 1.45 (m, 2H), 1.65 (m, 2H), 1.78 (d, J=13.53 Hz, 2H), 2.3 (d, J=6.92 Hz, 2H), 2.49 (m, 3H), 3.11 (d, J=9.91 Hz, 2H), 3.82 (s, 2H), 7.30 (t, J=7.55 Hz, 1H), 7.51 (t, J=7.55 Hz, 1H), 7.60 (d, J=7.87 Hz, 1H), 7.98 (d, J=7.87 Hz, 1H).

(iv). A solution of N-(2-methylpropyl)-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine (6.3 g, 0.02 mol) dissolved in isopropanol (70 ml), then L-tartaric acid (3 g, 0.02 mol) was added in one portion, then the mixture was heated up to 65°C. After 1h at 65°C the mixture was allowed to stir at room temperature for another 1h. The title compound (8.4g, 90% yield) was then isolated by filtration; washed twice with 10ml isopropanol, dried under vacuum up to 40°C. <sup>1</sup>H NMR (400 MHz, DMSO-D<sub>6</sub>) δ ppm 0.81 (d, J=6.57 Hz, 6H), 1.58 (m, 1H), 1.73 (m, 2H), 1.83 (m, 2H), 2.24 (d, J=7.07, 2H), 2.71 (t, J=11.62 Hz, 1H), 2.79 (m, 2H), 3.29 (d, J=12.13 Hz, 2H), 3.76 (s, 2H), 3.96 (s, 2H), 4.60 (s, 5H), 7.44 (t, J=7.45 Hz, 1H), 7.66 (m, 1H), 7.67 (d, J=7.83 Hz, 1H), 7.90 (d, J=8.08 Hz, 1H). <sup>13</sup>C NMR (250 MHz, DMSO-D<sub>6</sub>) δ ppm: 20.94, 24.72, 26.63, 43.53, 51.01, 55.34, 58.64, 72.00, 125.78, 126.77, 127.12, 127.24, 127.38, 130.28, 132.78, 140.10, 174.90.

### 20 EXAMPLE 3:

#### N-(1-methylethyl)-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine fumarate



(i) Sodium triacetoxyborohydride (0.5g, 2.36mmol) was added to a mixture of 1,1-dimethylethyl 4-({2-(trifluoromethyl)phenyl}methyl)amino)piperidine-1-carboxylate (0.6g, 1.68mmol), acetone (0.39g, 6.70mmol), acetic acid (1.01g, 16.7 mmol) and 1,2-dichloroethane. After stirring under nitrogen at room temperature for 15 min, the mixture was heated at 55°C for 3 days. More acetone (0.30g, 6.7mmol) and sodium

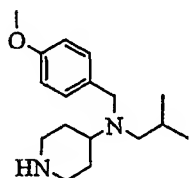
-50-

triacetoxyborohydride (0.5g, 2.36mmol) were added and the mixture was reheated for 2 days. After cooling, water (10ml) and excess 5M NaOH solution were added and, after stirring at room temperature for 30 min, the product was extracted into dichloromethane. The dichloromethane extract was washed (brine), dried (MgSO<sub>4</sub>) and evaporated in vacuo to give an oil (0.55g). The oil was purified by MS guided preparative LC to give 1,1-dimethylethyl 4-((2-methylpropyl){[2-(trifluoromethyl)phenyl]methyl}amino)piperidine-1-carboxylate as the acetate salt (0.082g, 12%); LCMS 6 min, Rt = 3.96 min, (M<sup>+</sup>+H) = 401.

(ii) 4M HCl in dioxane (1ml) was added to 1,1-dimethylethyl 4-((2-methylpropyl){[2-(trifluoromethyl)phenyl]methyl}amino)piperidine-1-carboxylate acetate salt (82mg, 0.16mmol) in ethanol (5ml). After stirring for 6h at room temperature, the solution was evaporated in vacuo at 50°C to give an oil which was converted to the free base using a SCX-2 ion exchange column, eluting with methanol and then a 2.3M solution of ammonia in methanol. The free base was converted to the fumarate salt (ethanol/ether) to give the title product as a white solid (43.3mg, 65%).  $\delta_H$  (300 MHz, MeOD) 8.12-8.19 (1H, d), 7.70-7.78 (2H, dd), 7.48-7.53 (1H, t), 6.82 (2H, s), 4.06 (2H, s), 3.51-3.55 (2H, bd), 3.20-3.29 (1H, quintet), 3.06-3.15 (3H, m), 2.12-2.22 (2H, br d), 1.84-1.97 (2H, m), 1.22-1.24 (6H, d). LCMS 12 min, Rt = 4.67 min, (M<sup>+</sup>+H) = 301.

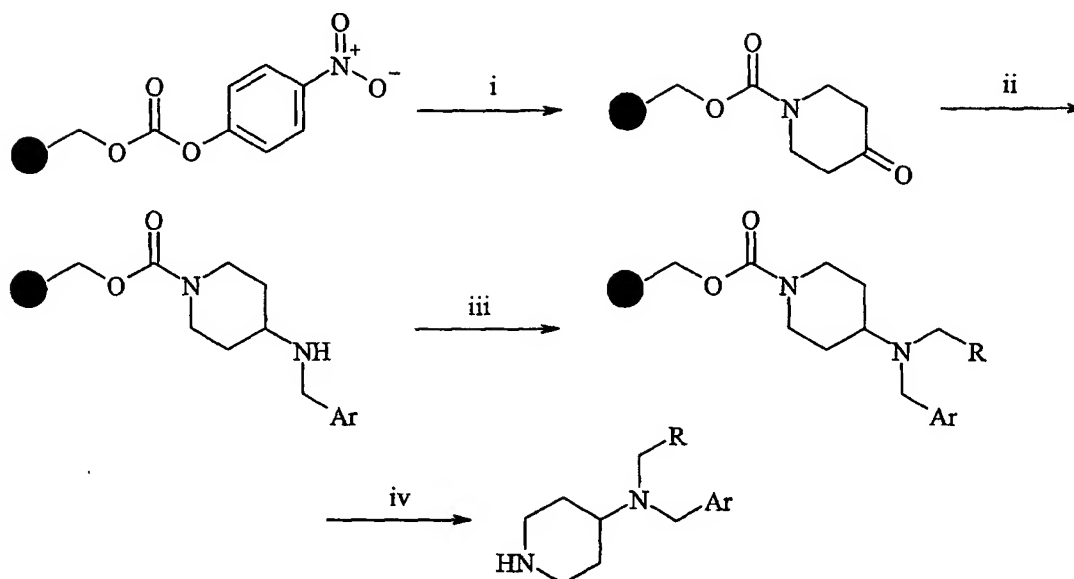
#### 20 EXAMPLE 4:

##### N-(2-methylpropyl)-N-{[4-(methoxy)phenyl]methyl}piperidin-4-amine



Compounds were prepared by solid phase synthesis by the route shown below. The sequence is preferably performed on a polystyrene resin. The process may be run in a combinatorial fashion such that all possible compounds from sets of precursors ArCH<sub>2</sub>NH<sub>2</sub> and RCHO may be prepared. The sequence is performed without characterisation of the resin-bound intermediates.

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i) To suspension of p-nitrophenyl carbonate resin (Novabiochem, 1.56 g, 1.5 mmol) in DMF (20 ml) was added 4-piperidone hydrate hydrochloride (691 mg, 4.5 mmol) and N,N-diisopropylethylamine (1.56 ml, 9 mmol). The mixture was agitated gently for 69 h, then filtered and washed with DMF (3 x 50 ml). The resin was resuspended in DMF (20 ml), N,N-diisopropylethylamine (2 ml) added, and the mixture agitated gently for 5 min. The resin was filtered off, washed with DMF (2 x 50 ml) and MeOH (3 x 50 ml) and dried in a vacuum oven at 45°C.

(ii) Aliquots (50 mg, 0.05 mmol) of the resin prepared in step i) were dispensed into a Titan 24-well Filter Plate (Radleys) fitted with 5 mm PTFE frits. The bottom of the filter plate was closed with a PTFE seal retained by a Combi-Clamp (Radleys). To each well was added a 1M solution of a substituted benzylamine in DMF (0.5 ml, 0.5 mmol) and a 0.5M solution of sodium triacetoxyborohydride in DMF (0.5 ml, 0.25 mmol). The top of the plate was closed with a PTFE seal retained by the Combi-Clamp and the whole assembly agitated by orbital shaking for 22 h. After removal of the seals the reactions were filtered under a slight vacuum and washed with DMF (4 x 2.5 ml).

(iii) The bottom of the filter plate was closed with a PTFE seal retained by a Combi-Clamp. To each well was added a 1M solution of an aldehyde in DMF (0.5 ml, 0.5 mmol) and a 0.5M solution of sodium triacetoxyborohydride in DMF (0.5 ml, 0.25 mmol). The top of the plate was closed with a PTFE seal retained by the Combi-Clamp and the whole assembly agitated by orbital shaking for 43 h. After removal of the seals

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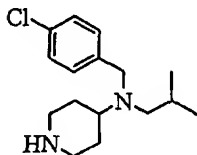
the reactions were filtered under a slight vacuum and washed with DMF (1 x 2.5 ml), EtOH (2 x 2.5 ml) and dichloromethane (4 x 2.5 ml), and partially dried under vacuum.

(iv) The bottom of the filter plate was closed with a PTFE seal retained by a Combi-Clamp. To each well was added a TFA/H<sub>2</sub>O mixture (95:5 v/v, 1 ml). The top of the plate was closed with a PTFE seal retained by the Combi-Clamp and the whole assembly agitated by orbital shaking for 6 h. After removal of the seals the reactions were filtered under a slight vacuum and washed with dichloromethane (2 x 2 ml). Appropriate filtrates and washings were combined and volatile components removed by vacuum evaporation. Each residue was dissolved in MeOH (1 ml) and the solutions applied to MeOH-washed SCX-2 cartridges (0.5 g/2.5 ml) (Jones Chromatography). After draining under gravity the cartridges were washed with MeOH (2.5 ml) and the products then eluted using a 2M solution of ammonia in MeOH (2.5 ml). Removal of volatile components by vacuum evaporation gave the desired products in ca. 50% overall yield.

By this means using 4-methoxybenzylamine and isobutyraldehyde was prepared the title compound N-(2-methylpropyl)-N-[[4-(methoxy)phenyl]methyl]-piperidin-4-amine, m/e 277.2 [M+H],  $\delta$ H (300 MHz CDCl<sub>3</sub>) 7.26-7.23 (2H d Ar), 6.84-6.81 (2H d Ar), 3.80 (3H s CH<sub>3</sub>OAr), 3.54 (2H s ArCH<sub>2</sub>N), 3.11-3.07 (2H d CH<sub>2</sub>NH), 2.52-2.45 (3H m CH<sub>2</sub>N), 2.22-2.19 (2H d iPrCH<sub>2</sub>N), 1.84-1.63 (3H m ring CH<sub>2</sub>, Me<sub>2</sub>CH), 1.60-1.36 (2H m ring CH<sub>2</sub>), 0.84-0.82 (6H d CH<sub>3</sub>CH).

#### **EXAMPLE 5:**

##### **N-(2-methylpropyl)-N-[[4-(chloro)phenyl]methyl]piperidin-4-amine**

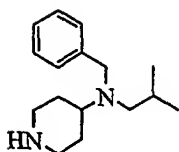


The title product m/e 281.1 (M+H) was prepared by the method described in example 4.

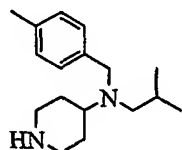
#### **EXAMPLE 6:**

##### **N-(2-methylpropyl)-N-(phenylmethyl)piperidin-4-amine**

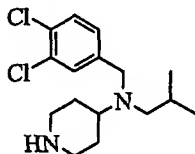
-53-



The title product m/e 247.2 (M+H) was prepared by the method described in example 4.

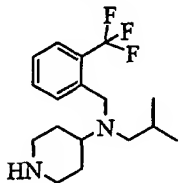
**EXAMPLE 7:****N-(2-methylpropyl)-N-{[4-(methyl)phenyl]methyl}piperidin-4-amine**

- 5 The title product m/e 261.2 (M+H) was prepared by the method described in example 4.

**EXAMPLE 8:****N-(2-methylpropyl)-N-{[3,4-(dichloro)phenyl]methyl}piperidin-4-amine**

The title product m/e 315.1 (M+H) was prepared by the method described in example 4.

10

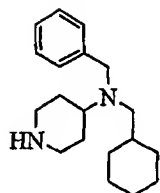
**EXAMPLE 9:****N-(2-methylpropyl)-N-{[2-(trifluoromethyl)phenyl]methyl}piperidin-4-amine**

The title product m/e 315.2 (M+H) was prepared by the method described in example 4.

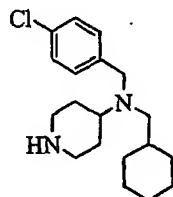
- 15 **EXAMPLE 10:**

**N-(cyclohexylmethyl)-N-(phenylmethyl)piperidin-4-amine**

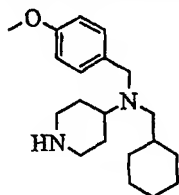
-54-



The title product m/e 287.2 (M+H) was prepared by the method described in example 4.

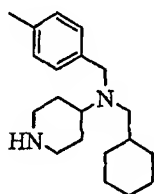
**EXAMPLE 11:****N-(cyclohexylmethyl)-N-{[4-(chloro)phenyl]methyl}piperidin-4-amine**

- 5 The title product m/e 321.2 (M+H) was prepared by the method described in example 4.

**EXAMPLE 12:****N-(cyclohexylmethyl)-N-{[4-(methoxy)phenyl]methyl}piperidin-4-amine**

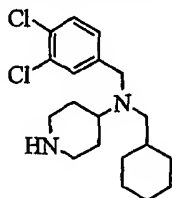
The title product m/e 317.2 (M+H) was prepared by the method described in example 4.

10

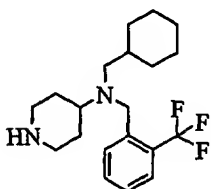
**EXAMPLE 13:****N-(cyclohexylmethyl)-N-{[4-(methyl)phenyl]methyl}piperidin-4-amine**

The title product m/e 301.2 (M+H) was prepared by the method described in example 4.

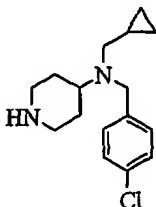
-55-

**EXAMPLE 14:****N-(cyclohexylmethyl)-N-{{3,4-(dichloro)phenyl}methyl}piperidin-4-amine**

The title product m/e 355.1 (M+H) was prepared by the method described in example 4.

5 **EXAMPLE 15:****N-(cyclohexylmethyl)-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine**

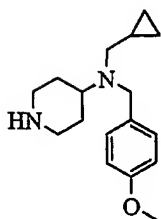
The title product m/e 355.2 (M+H) was prepared by the method described in example 4.

**EXAMPLE 16:**10 **N-(cyclopropylmethyl)-N-{{4-(chloro)phenyl}methyl}piperidin-4-amine**

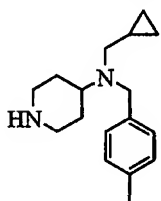
The title product m/e 279.1 (M+H) was prepared by the method described in example 4.

**EXAMPLE 17:****N-(cyclopropylmethyl)-N-{{4-(methoxy)phenyl}methyl}piperidin-4-amine**

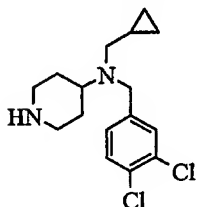
-56-



The title product m/e 275.2 (M+H) was prepared by the method described in example 4.

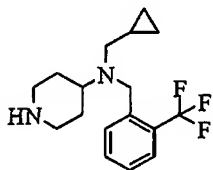
**EXAMPLE 18:****N-(cyclopropylmethyl)-N-{[4-(methyl)phenyl]methyl}piperidin-4-amine**

- 5 The title product m/e 259.1 (M+H) was prepared by the method described in example 4.

**EXAMPLE 19:****N-(cyclopropylmethyl)-N-{[3,4-(dichloro)phenyl]methyl}piperidin-4-amine**

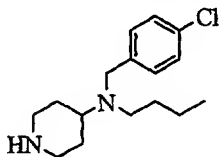
The title product m/e 313.1 (M+H) was prepared by the method described in example 4.

10

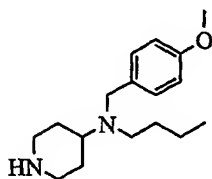
**EXAMPLE 20:****N-(cyclopropylmethyl)-N-{[2-(trifluoromethyl)phenyl]methyl}piperidin-4-amine**

The title product m/e 313.2 (M+H) was prepared by the method described in example 4.

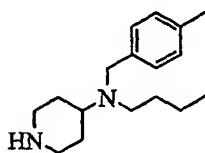


**EXAMPLE 21:****N-(butyl)-N-{[4-(chloro)phenyl]methyl}piperidin-4-amine**

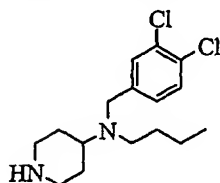
The title product m/e 281.1 (M+H) was prepared by the method described in example 4.

5 **EXAMPLE 22:****N-(butyl)-N-{[4-(methoxy)phenyl]methyl}piperidin-4-amine**

The title product m/e 277.2 (M+H) was prepared by the method described in example 4.

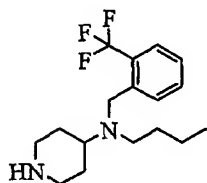
**EXAMPLE 23:**10 **N-(butyl)-N-{[4-(methyl)phenyl]methyl}piperidin-4-amine**

The title product m/e 261.2 (M+H) was prepared by the method described in example 4.

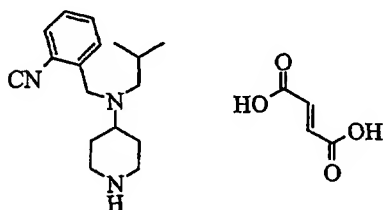
**EXAMPLE 24:****N-(butyl)-N-{[3,4-(dichloro)phenyl]methyl}piperidin-4-amine**

15 The title product m/e 315.1 (M+H) was prepared by the method described in example 4.

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**EXAMPLE 25:****N-(butyl)-N-{[2-(trifluoromethyl)phenyl]methyl}piperidin-4-amine**

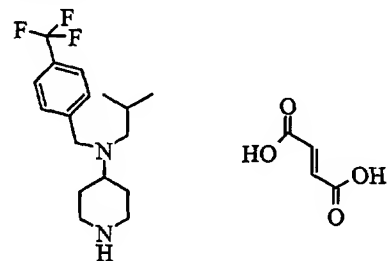
The title product  $m/e$  315.2 (M+H) was prepared by the method described in example 4.

5 **EXAMPLE 26:****N-(2-methylpropyl)-N-{[2-(cyano)phenyl]methyl}piperidin-4-amine fumarate**

To a solution of 1,1-dimethylethyl 4-[(2-methylpropyl)amino]piperidine-1-carboxylate (0.38 g, 1.5 mmol, 1 eq) in 1,2-dichloroethane (10ml) was added 2-cyanobenzaldehyde (295 mg, 2.25 mmol, 1.5 eq) in 1,2-dichloroethane (1 ml). After stirring for 15 minutes sodium triacetoxyborahydride (0.48g, 2.25 mmol, 1.5 eq) was added and the mixture left to stir for a further for 48 h. A further portion of 2-cyanobenzaldehyde (295 mg, 2.25 mmol, 1.5 eq) in 1,2-dichloroethane (1 ml) and sodium triacetoxyborahydride (0.48g, 2.25 mmol, 1.5 eq) in dimethylformamide (2 ml) were added and the reaction stirred for a further 16 h. Methanol (10 ml) was added and the product purified using SCX-2 ion exchange cartridge (2 x 10 g) washing with methanol (100 ml) and eluting the product with 2M ammonia in methanol solution (100 ml). The solvent removed *in vacuo* to give 1,1-dimethylethyl 4-[[2-(2-cyanophenyl)methyl](2-methylpropyl)amino]-piperidine-1-carboxylate as a colourless oil. To this oil was added a 95% trifluoroacetic acid in water solution (10 ml) and the mixture stirred at room temperature for 16 h. The solvent removed *in vacuo* and the residue diluted with methanol (5 ml) and loaded onto SCX-2 ion exchange cartridge (5 g). The column was washed with methanol (15 ml) and eluting the product with 2M ammonia in methanol solution (15 ml) the solvent removed *in vacuo* to give (309 mg, 76%) as a colourless oil. The product was taken up in diethyl ether (15

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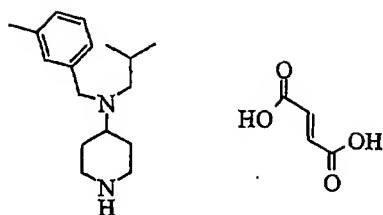
ml) and a few drops of methanol to solubilise and a hot solution of fumaric acid (132 mg, 1.1 mmol, 1 eq) in methanol (1 ml) was added. The solution was heated and a few drops of methanol added until all solid was in solution, then the mixture was allowed to slowly cool to 0°C. The product was collected by filtration and dried in a vacuum oven (40°C for 2 h) to give N-(2-methylpropyl)-N-{{2-(cyano)phenyl}methyl}piperidin-4-amine fumarate (279 mg, 48%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 7.71 (1H, d,  $J = 7.5$  Hz, ArH), 7.65-7.64 (2H, m, ArH), 7.47-7.41 (1H, m, ArH), 6.70 (2H, s, fumarate CH), 3.86 (2H, s,  $CH_2Ar$ ), 3.50-3.46 (2H, m,  $NCH_2$ ), 3.03-2.85 (3H, m, NCH,  $NCH_2$ ), 2.30 (2H, d,  $J = 7.2$  Hz,  $NCH_2$ ), 2.13-2.09 (2H, m,  $CCH_2$ ), 1.90-1.75 (2H, m,  $CCH_2$ ), 1.63-1.54 (1H, m,  $CH(CH_3)_2$ ) and 0.81 (6H, d,  $J = 6.6$  Hz,  $CH_3$ ); LCMS 12 min,  $R_t = 4.4$  min,  $(M^+ + 1) = 272.2$ .

**EXAMPLE 27:****N-(2-methylpropyl)-N-{{4-(trifluoromethyl)phenyl}methyl}piperidin-4-amine fumarate**

As example 26 with 1,1-dimethylethyl 4-[(2-methylpropyl)amino]piperidine-1-carboxylate and 4-(trifluoromethyl)benzaldehyde to give N-(2-methylpropyl)-N-{{4-(trifluoromethyl)phenyl}methyl}piperidin-4-amine fumarate (242 mg, 37%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 7.63-7.56 (4H, m, ArH), 6.70 (2H, s, fumarate CH), 3.76 (2H, s,  $CH_2Ar$ ), 3.46-3.42 (2H, m,  $NCH_2$ ), 2.98-2.77 (3H, m, NCH,  $NCH_2$ ), 2.31 (2H, d,  $J = 7.2$  Hz,  $NCH_2$ ), 2.05-2.00 (2H, m,  $CCH_2$ ), 1.84-1.66 (3H, m,  $CCH_2$  and  $CH(CH_3)_2$ ) and 0.89 (6H, d,  $J = 6.6$  Hz,  $CH_3$ ); LCMS 12 min,  $R_t = 4.15$  min,  $(M^+ + 1) = 315.2$

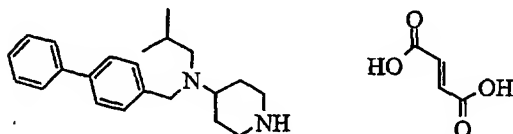
**EXAMPLE 28:****N-(2-methylpropyl)-N-{{3-(methyl)phenyl}methyl}piperidin-4-amine fumarate**

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As example 26 with 1,1-dimethylethyl 4-[(2-methylpropyl)amino]piperidine-1-carboxylate and 3-methylbenzaldehyde, further purification by recrystallisation from diethyl ether and ethanol gave N-(2-methylpropyl)-N-[[3-(methyl)phenyl]methyl]piperidin-4-amine fumarate (156 mg, 28%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 7.21-7.14 (3H, m, ArH), 7.10-7.03 (1H, m, ArH), 6.70 (2H, s, fumarate CH), 3.64 (2H, s, CH<sub>2</sub>Ar), 3.45-3.41 (2H, m, NCH<sub>2</sub>), 2.95-2.77 (3H, m, NCH, NCH<sub>2</sub>), 2.33 (3H, s, CH<sub>3</sub>), 2.28 (2H, d, J = 7.1 Hz, NCH<sub>2</sub>), 2.02-1.98 (2H, m, CCH<sub>2</sub>), 1.83-1.66 (3H, m, CCH<sub>2</sub> and CH(CH<sub>3</sub>)<sub>2</sub>) and 0.89 (6H, d, J = 6.6 Hz, CH<sub>3</sub>); LCMS 12 min, Rt = 1.32 min, (M<sup>+</sup>+1) = 261.3.

10

**EXAMPLE 29:****N-(2-methylpropyl)-N-[[4-(phenyl)phenyl]methyl]piperidin-4-amine fumarate**

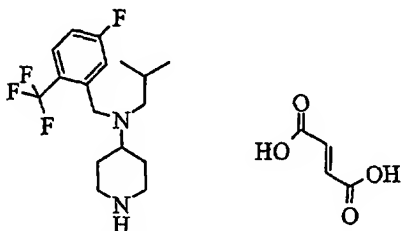
As example 26 with 1,1-dimethylethyl 4-[(2-methylpropyl)amino]piperidine-1-carboxylate and 4-biphenylcaroxaldehyde to give N-(2-methylpropyl)-N-[[4-(phenyl)phenyl]methyl]piperidin-4-amine fumarate (208 mg, 32%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 7.63-7.56 (4H, m, ArH), 7.46-7.41 (4H, m, ArH), 7.35-7.30 (1H, m, ArH), 6.70 (2H, s, fumarate CH), 3.72 (2H, s, CH<sub>2</sub>Ar), 3.46-3.42 (2H, m, NCH<sub>2</sub>), 2.97-2.81 (3H, m, NCH, NCH<sub>2</sub>), 2.33 (2H, d, J = 7.2 Hz, NCH<sub>2</sub>), 2.05-2.01 (2H, m, CCH<sub>2</sub>), 1.85-1.72 (3H, m, CCH<sub>2</sub> and CH(CH<sub>3</sub>)<sub>2</sub>) and 0.92 (6H, d, J = 6.6 Hz, CH<sub>3</sub>); LCMS 12 min, Rt = 4.08 min, (M<sup>+</sup>+1) = 323.2.

20

**EXAMPLE 30:**

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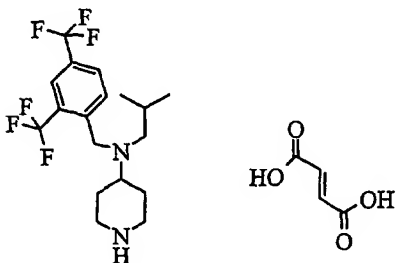
**N-(2-methylpropyl)-N-{{5-fluoro-2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine fumarate**



As example 26 with 1,1-dimethylethyl 4-[(2-methylpropyl)amino]piperidine-1-carboxylate and 5-fluoro-2-(trifluoromethyl)benzaldehyde, further purification by recrystallisation from diethyl ether and ethanol gave N-(2-methylpropyl)-N-{{5-fluoro-2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine fumarate (160 mg, 24%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 7.51-7.48 (2H, m, ArH), 6.96-6.91 (1H, m, ArH), 6.48 (2H, s, fumarate CH), 3.65 (2H, s,  $CH_2Ar$ ), 3.26-3.22 (2H, m,  $NCH_2$ ), 2.79-2.59 (3H, m, NCH,  $NCH_2$ ), 2.13 (2H, d,  $J = 7.0$  Hz,  $NCH_2$ ), 1.86-1.82 (2H, m,  $CCH_2$ ), 1.61-1.42 (3H, m,  $CCH_2$  and  $CH(CH_3)_2$ ) and 0.71 (6H, d,  $J = 6.6$  Hz,  $CH_3$ ); LCMS 12 min,  $R_t = 6.08$  min,  $(M^+ + 1) = 333.1$ .

**EXAMPLE 31:**

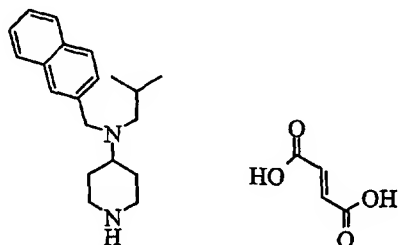
**N-(2-methylpropyl)-N-{{2,4-di-(trifluoromethyl)phenyl}methyl}piperidin-4-amine fumarate**



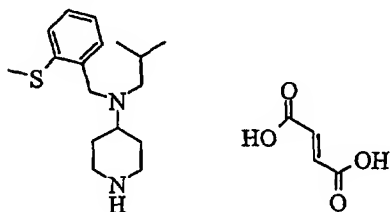
As example 26 with 1,1-dimethylethyl 4-[(2-methylpropyl)amino]piperidine-1-carboxylate and 2,4-bis(trifluoromethyl)benzaldehyde to give N-(2-methylpropyl)-N-{{2,4-di-(trifluoromethyl)phenyl}methyl}piperidin-4-amine fumarate (249 mg, 33%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 8.23 (1H, d,  $J = 8.1$  Hz, ArH), 7.97-7.93 (2H, m, ArH), 6.70 (2H, s, fumarate CH), 3.95 (2H, s,  $CH_2Ar$ ), 3.48-3.44 (2H, m,  $NCH_2$ ), 3.00-2.78 (3H, m, NCH,  $NCH_2$ ), 2.36 (2H, d,  $J = 7.2$  Hz,  $NCH_2$ ), 2.08-2.04 (2H, m,  $CCH_2$ ),

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1.86-1.63 (3H, m, CCH<sub>2</sub> and CH(CH<sub>3</sub>)<sub>2</sub>) and 0.92 (6H, d, J = 6.6 Hz, CH<sub>3</sub>); LCMS 12 min, Rt = 6.74 min, (M<sup>+</sup>+1) = 383.1.

**EXAMPLE 32:**5 **N-(2-methylpropyl)-N-{[2-naphthyl]methyl}piperidin-4-amine fumarate**

As example 26 with 1,1-dimethylethyl 4-[(2-methylpropyl)amino]piperidine-1-carboxylate and 2-naphthaldehyde to give N-(2-methylpropyl)-N-{[2-naphthyl]methyl}piperidin-4-amine fumarate (227 mg, 37%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 7.85-7.79 (4H, m, ArH), 7.56-7.53 (1H, m, ArH), 7.50-7.42 (2H, m, ArH),  
 10 6.70 (2H, s, fumarate CH), 3.84 (2H, s, CH<sub>2</sub>Ar), 3.45-3.41 (2H, m, NCH<sub>2</sub>), 2.94-2.82 (3H, m, NCH, NCH<sub>2</sub>), 2.35 (2H, d, J = 7.1 Hz, NCH<sub>2</sub>), 2.08-2.03 (2H, m, CCH<sub>2</sub>), 1.87-1.71 (3H, m, CCH<sub>2</sub> and CH(CH<sub>3</sub>)<sub>2</sub>) and 0.91 (6H, d, J = 6.6 Hz, CH<sub>3</sub>); LCMS 12 min, Rt = 3.46 min, (M<sup>+</sup>+1) = 297.2.

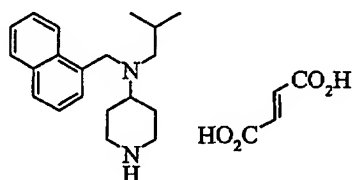
15 **EXAMPLE 33:****N-(2-methylpropyl)-N-{[2-(methylthio)phenyl]methyl}piperidin-4-amine fumarate**

As example 26 with 1,1-dimethylethyl 4-[(2-methylpropyl)amino]piperidine-1-carboxylate and 2-methylthiobenzaldehyde, further purification by recrystallisation from diethyl ether and ethanol gave N-(2-methylpropyl)-N-{[2-(methylthio)phenyl]methyl}piperidin-4-amine fumarate (172 mg, 28%) as a white solid.  
 20  $\delta_H$  (300 MHz, MeOD) 7.44 (1H, d, J = 7.7 Hz, ArH), 7.29-7.22 (2H, m, ArH), 7.15-7.10

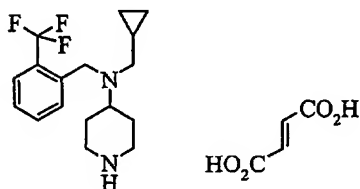
-63-

(1H, m, ArH), 6.70 (2H, s, fumarate CH), 3.75 (2H, s, CH<sub>2</sub>Ar), 3.47-3.42 (2H, m, NCH<sub>2</sub>), 2.96-2.77 (3H, m, NCH, NCH<sub>2</sub>), 2.46 (3H, s, SCH<sub>3</sub>), 2.29 (2H, d, J = 7.0 Hz, NCH<sub>2</sub>), 2.08-2.03 (2H, m, CCH<sub>2</sub>), 1.87-1.60 (3H, m, CCH<sub>2</sub> and CH(CH<sub>3</sub>)<sub>2</sub>) and 0.86 (6H, d, J = 6.6 Hz, CH<sub>3</sub>); LCMS 12 min, Rt = 2.92 min, (M<sup>+</sup>+1) = 293.2.

5

**EXAMPLE 34:****N-(2-methylpropyl)-N-[[1-naphthyl]methyl]piperidin-4-amine hemifumarate**

As example 26 with 1,1-dimethylethyl 4-[(2-methylpropyl)amino]piperidine-1-carboxylate and 1-naphthaldehyde, further purification by recrystallisation from diethyl ether and ethanol gave N-(2-methylpropyl)-N-[[1-naphthyl]methyl]piperidin-4-amine hemifumarate (170 mg, 27%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 8.44-8.41 (1H, m, ArH), 7.97-7.86 (2H, m, ArH), 7.66-7.49 (4H, m, ArH), 6.75 (1H, s, fumarate CH), 4.24 (2H, s, CH<sub>2</sub>Ar), 3.51-3.47 (2H, m, NCH<sub>2</sub>), 2.96-2.88 (3H, m, NCH, NCH<sub>2</sub>), 2.46 (2H, d, J = 7.2 Hz, NCH<sub>2</sub>), 2.15-2.10 (2H, m, CCH<sub>2</sub>), 1.98-1.71 (3H, m, CCH<sub>2</sub> and CH(CH<sub>3</sub>)<sub>2</sub>) and 0.92 (6H, d, J = 6.6 Hz, CH<sub>3</sub>); LCMS 12 min, Rt = 3.96 min, (M<sup>+</sup>+1) = 297.2.

**EXAMPLE 35:****N-(cyclopropylmethyl)-N-[[2-(trifluoromethyl)phenyl]methyl]piperidin-4-amine fumarate**

(i) To a solution of 1,1-dimethylethyl 4-([2-(trifluoromethyl)phenyl]methyl)amino)piperidine-1-carboxylate (8g, 22.3 mmol, 1 eq) in 1,2-dichloroethane (125 ml) was added cyclopropane carboxaldehyde (5.4 ml, 72.2 mmol, mmol, 3.2 eq). After stirring for 15 minutes sodium triacetoxymethylborohydride (6.62

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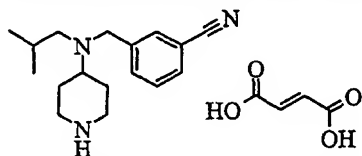
g, 31.2 mmol, 1.4 eq) was added and the mixture in two portions and left to stir for 16 h. 2M aqueous sodium hydroxide was added (50 ml), the aqueous layer was separated and extracted with dichloromethane (3 x 100 ml). The combined organic extracts were dried (MgSO<sub>4</sub>) and the solvent removed *in vacuo* to give a colourless oil which was purified by  
5 flash chromatography with 10% ethyl acetate in *iso*-hexane to give 1,1-dimethylethyl 4-  
[{{2-(trifluoromethyl)phenyl}methyl}(cyclopropylmethyl)amino]-piperidine-1-  
carboxylate (6.6 g, 72%) as a white crystalline solid.  $\delta_H$  (300 MHz, MeOD) 8.01 (1H, d, J  
= 7.8 Hz, ArH), 7.58 (1H, d, J = 7.8 Hz, ArH), 7.53-7.48 (1H, m, ArH), 7.31-7.29 (1H, m,  
ArH), 4.21-4.04 (2H, m, NCH<sub>2</sub>), 3.86 (2H, s, CH<sub>2</sub>Ar), 2.83-2.50 (3H, m, NCH, NCH<sub>2</sub>),  
10 2.40 (2H, d, J = 6.4 Hz, NCH<sub>2</sub>), 1.80-1.69 (2H, m, CCH<sub>2</sub>), 1.50-1.31 (11H, m, CCH<sub>2</sub> and  
C(CH<sub>3</sub>)<sub>3</sub>), 0.89-0.70 (1H, m, CH), 0.43-0.33 (2H, m, CH<sub>2</sub>) and 0.09-0.00 (2H, m, CH<sub>2</sub>);  
LCMS 6 min, Rt = 3.54 min, (M<sup>+</sup>+1) = 413.3.

(ii) To a solution of 1,1-dimethylethyl 4-[[2-(trifluoromethyl)phenyl]methyl}(cyclopropylmethyl)amino]-piperidine-1-carboxylate  
15 (6.6 g, 16 mmol, 1 eq) in ethanol (20 ml) was added a solution of concentrated  
hydrochloric acid (41.1 ml, 480 mmol, 30 eq) in ethanol (80 ml) and the solution left to  
stir at room temperature for 120 h. The solvent removed *in vacuo* and the oil taken up in  
dichloromethane (50 ml) and washed with saturated potassium carbonate (100 ml). The  
aqueous layer was separated and extracted with dichloromethane (3 x 50 ml), the  
20 combined organic extracts were dried (MgSO<sub>4</sub>) and the solvent removed *in vacuo*. The  
residue was purified by flash chromatography with a gradient of 50% ethanol in 5%  
ammonia in methanol to give (4.08 g, 82%) as a colourless oil. The product was taken up  
in diethyl ether (150 ml) and a few drops of methanol to solubilize and a hot solution of  
fumaric acid (1.5 g, 13.1 mmol, 1 eq) in methanol (10 ml) was added. The solution was  
25 heated and a few drops of methanol added until all solid was in solution, then the mixture  
was allowed to slowly cool to 0°C. The product was collected by filtration and  
recrystallised from ethyl acetate/ethanol mixture to give N-(cyclopropylmethyl)-N-[[2-(trifluoromethyl)phenyl]methyl]piperidin-4-amine fumarate (2.3 g, 34%) as a white solid.  
 $\delta_H$  (300 MHz, MeOD) 7.95 (1H, d, J = 7.7 Hz, ArH), 7.57-7.48 (2H, m, ArH), 7.33-7.28  
30 (1H, m, ArH), 6.60 (2H, s, fumarate CH), 3.86 (2H, s, CH<sub>2</sub>Ar), 3.38-3.34 (2H, m, NCH<sub>2</sub>),  
3.00-2.83 (3H, m, NCH, NCH<sub>2</sub>), 2.38 (2H, d, J = 6.4 Hz, NCH<sub>2</sub>), 2.00-1.95 (2H, m,



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CCH<sub>2</sub>), 1.77-1.62 (2H, m, CCH<sub>2</sub>), 0.79-0.72 (1H, m, CH), 0.39-0.33 (2H, m, CH<sub>2</sub>) and 0.02-0.00 (2H, m, CH<sub>2</sub>); LCMS 12 min, Rt = 3.56 min, (M<sup>+</sup>+1) = 313.1.

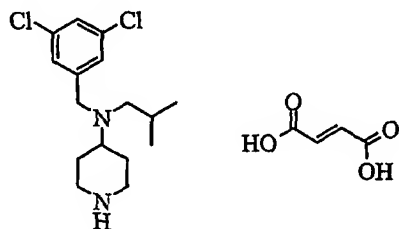
**EXAMPLE 36:****5 N-(2-methylpropyl)-N-[(3-cyanophenyl)methyl]piperidin-4-amine fumarate**

- (i) To 10% Pd/C (3.0 g, 10%wt), under nitrogen, was added a solution of the 1-Boc-4-piperidone (30 g, 150.56 mmol, 1.0 eq.) and isobutylamine (11.23 g, 180.3 mmol, 1.2 eq.) in ethanol (300 ml). This was hydrogenated for 1.5 h at 65 psi using a Parr hydrogenator. The catalyst was removed by filtration through Celite. Solvent was removed under vacuum to give 4-isobutylamino-piperidine-1-carboxylic acid tert-butyl ester as a colourless oil (31.2 g) with >98% purity. LCMS- 6 mins gradient Rt = 2.79 (M<sup>+</sup>+1) 257.2. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ= 4.01 (2H, brs), 2.75-2.82 (2H, m), 2.54-2.61 (1H, m), 2.43 (2H, d, J=12.4Hz), 1.81-1.85 (2H, m), 1.67-1.76 (1H, m), 1.56 (1H, br s), 1.45 (9H, s), 1.18-1.31 (2H, m), 0.91 (6H, d, J=6.4Hz).
- (ii) General method: To a solution of secondary amine (0.5 g, 1.0 eq) in 1,2-dichloroethane (10 ml) was added the desired benzaldehyde (3.0 eq.). To this was added a solution of sodium triacetoxyborohydride (3.0 eq.) in dimethylformamide (2 ml). This mixture was left to stir under nitrogen, at room temperature, for 3 days. To the reaction mixture was then added water (10 ml) and the mixture stirred vigorously for several minutes. The chlorinated organic layer was then run through a hydrophobic frit to remove water. The resulting organic solution was diluted with methanol (10 ml) and loaded onto an SCX-2 (10 g) column. The column was washed with methanol (20 ml) then basic material eluted with 2M ammonia in methanol (20 ml). The ammonia/methanol solution was concentrated *in vacuo* to give the N-Boc-piperidine product.
- To a solution of the oil (1.0 eq.) in dichloromethane (10 ml) was added trifluoroacetic acid (TFA) (15 eq). The solution was stirred at room temperature for 4h. The solvent and TFA were removed *in vacuo*. The resulting oil was taken up in methanol and loaded onto an SCX-2 (10 g) column. The column was washed with methanol (20 ml). Basic material

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was then eluted using 2M ammonia in methanol (20 ml). Removal of solvent from the ammonia/methanol mixture under vacuum, gave the desired compound as an oil. The oil was taken up in diethylether and a solution of fumaric acid (1 eq) in hot ethanol was added. The mixture was left at room temperature for a few minutes before precipitation  
5 occurred or if necessary the solution was placed in the fridge for a few hours. The resulting precipitate was collected by filtration to give the fumarate salt as a white solid.

The title product was prepared by the general method above using tert-butyl 4-isobutylamino-piperidine-1-carboxylate and 3-cyanobenzaldehyde. LCMS 12 mins  
10 gradient  $R_t = 2.69$  ( $M^+ + 1$ ) 272.1,  $^1H$  NMR ( $d_6$ -DMSO)  $\delta = 7.80$ -7.65 (3H, m), 7.60-7.51 (1H, m), 6.45 (2H, s), 3.61 (2H, s), 3.23 (2H, brd), 2.80-2.61 (3H, m), 2.20 (2H, d), 1.85-1.75 (2H, m), 1.70-1.52 (3H, m), 0.77 (6H, d,  $J = 6.9$ Hz).

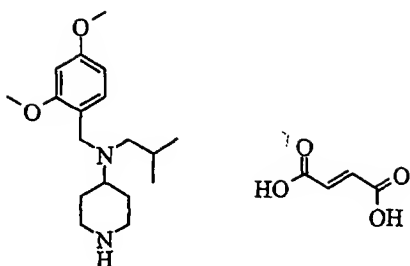
**EXAMPLE 37:****N-(2-methylpropyl)-N-[(3,5-dichlorophenyl)methyl]piperidin-4-amine fumarate**

15 The title product was prepared from tert-butyl 4-isobutylamino-piperidine-1-carboxylate and 3,5-dichlorobenzaldehyde using the method described in example 36. LCMS 12 mins gradient  $R_t = 5.38$  ( $M^+ + 1$ ) 315.1,  $^1H$  NMR ( $d_6$ -DMSO)  $\delta = 7.4$  (1H, s), 7.35 (2H, s), 6.35 (1H, s), 3.58 (2H, s), 3.15 (2H, brd), 2.75-2.55 (3H, m), 2.21 (2H, d), 1.85-1.45 (5H, m), 0.85 (6H, d,  $J = 6.4$ Hz).

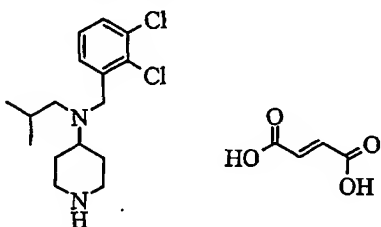
20

**EXAMPLE 38:****N-(2-methylpropyl)-N-[(2,4-dimethoxyphenyl)methyl]piperidin-4-amine fumarate**

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The title product was prepared from tert-butyl 4-isobutylamino-piperidine-1-carboxylate and 2,4-dimethoxybenzaldehyde using the method described in example 36. LCMS 12 mins gradient Rt = 2.03 ( $M^+ + 1$ ) 307.3.  $^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  = 7.23 (1H, d, J = 7.91Hz), 6.50 (2H, m), 6.45 (2H, s), 3.76 (3H, s, OMe), 3.75 (3H, s, OMe), 3.49 (2H, s),  
 5 3.25 (2H, brd), 2.80-2.61 (3H, m), 2.16 (2H, d, J = 6.97Hz), 1.77-1.58 (5H, m), 0.80 (6H, d, J = 6.41Hz).

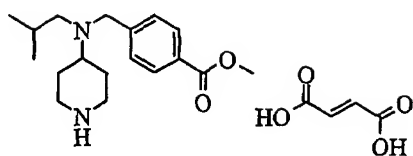
**EXAMPLE 39:****N-(2-methylpropyl)-N-[(2,3-dichlorophenyl)methyl]piperidin-4-amine fumarate**

10 The title product was prepared from tert-butyl 4-isobutylamino-piperidine-1-carboxylate and 2,3-dichlorobenzaldehyde using the method described in example 36. LCMS 12 mins gradient Rt = 5.34 ( $M^+ + 1$ ) 315.2.  $^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  = 7.57-7.51 (2H, m), 7.40-7.33 (1H, m), 6.47 (2H, s), 3.71 (2H, s), 3.25 (2H, brd), 2.85-2.63 (4H, m), 2.30 (2H, d, J = 6.97Hz), 1.85-1.52 (5H, m), 0.80 (6H, d, J = 6.59Hz).

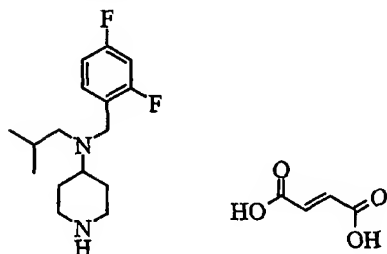
15

**EXAMPLE 40:****N-(2-methylpropyl)-N-[[4-(methoxycarbonyl)phenyl]methyl]piperidin-4-amine fumarate**

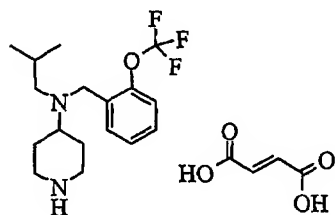
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The title product was prepared from tert-butyl 4-isobutylamino-piperidine-1-carboxylate and methyl 4-formylbenzoate using the method described in example 36. LCMS 12 mins gradient Rt= 2.99 ( $M^+ + 1$ ) 305.2.  $^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$ = 7.90 (2H, d,  $J$ = 8.29Hz), 7.40 (2H, d,  $J$ =8.29Hz), 6.60 (2H, s), 4.08 (3H, s), 3.84 (2H, s), 3.30 (2H, brd), 2.84-2.65 (4H, m), 2.49 (1H, s), 2.20 (2H, brd), 1.70-1.59 (4H, m), 0.79 (6H, d,  $J$ =6.6Hz).

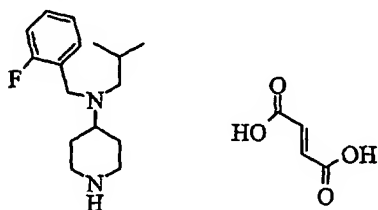
**EXAMPLE 41:****N-(2-methylpropyl)-N-[(2,4-difluorophenyl)methyl]piperidin-4-amine fumarate**

The title product was prepared from tert-butyl 4-isobutylamino-piperidine-1-carboxylate and 2,4-difluorobenzaldehyde using the method described in example 36. LCMS 12 mins gradient Rt = 2.79 ( $M^+ + 1$ ) 283.2.  $^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$ = 7.52-7.44 (1H, m), 7.19-7.12 (1H, m), 7.08-7.01 (1H, m), 6.42 (2H, s), 3.57 (2H, s), 3.22 (2H, brd), 2.78-2.62 (4H, m), 2.18 (2H, d), 1.79-1.53 (5H, m), 0.75 (6H, d,  $J$ =6.9Hz).

**EXAMPLE 42:****N-(2-methylpropyl)-N-[[2-(trifluoromethoxy)phenyl]methyl]piperidin-4-amine fumarate**

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The title product was prepared from tert-butyl 4-isobutylamino-piperidine-1-carboxylate and 2-(trifluoromethoxy)benzaldehyde using the method described in example 36. LCMS 12 mins gradient Rt = 4.45 ( $M^+ + 1$ ) 331.2.  $^1H$  NMR ( $d_6$ -DMSO)  $\delta$  = 7.64-7.60 (1H, m), 7.40-7.37 (2H, m), 7.36-7.31 (1H, m), 6.42 (2H, s), 3.63 (2H, s), 3.23 (2H, brd),  
5 2.76-2.62 (4H, m), 2.20 (2H, d,  $J$  = 6.97Hz), 1.80-1.61 (3H, m), 1.59-1.52 (2H, m), 0.61 (6H, d,  $J$  = 6.6Hz).

**EXAMPLE 43:****N-(2-methylpropyl)-N-[(2-fluorophenyl)methyl]piperidin-4-amine fumarate**

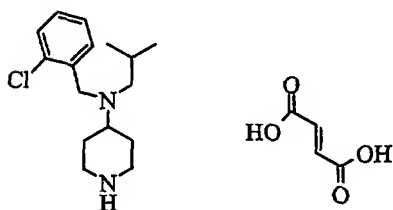
10 To a dry boiling tube (50 ml), under nitrogen, was added tert-butyl-4-(2-methylpropylamino)-piperidine-1-carboxylate (0.200g, 0.780 mmol), 2-fluorobenzaldehyde (0.087 ml, 0.102g, 0.819 mmol), and titanium isopropoxide (0.268 ml, 0.937 mmol) to give a yellow/orange solution. This was heated to 90°C for 2 hours. Solution cooled, and ethanol (5 ml) added. Sodium borohydride (0.030g, 0.780 mmol) was then added and  
15 allowed to stir for 2 days. Further sodium borohydride (0.300g, 7.80 mmol) was added, and after 6 hours, this was diluted with methanol (10 ml) with stirring for 20 hours. This was concentrated in vacuo, dissolved in dichloromethane (5 ml), and acetic anhydride (0.371 ml, 39.00 mmol) added with stirring for 30 minutes. Solution was diluted with methanol (10 ml), and passed through an SCX-2 column to give an oil (0.150g, 0.412  
20 mmol).

The resultant oil was dissolved in dichloromethane (5 ml), and trifluoroacetic acid (2 ml) added. Reaction was monitored by thin layer chromatography (100% ethyl acetate; reactant. r.f. 0.4, product r.f. 0.0). After 2 hours, reaction was concentrated in vacuo, azeotroped with dichloromethane (c.a. 25 ml), taken up in methanol (c.a. 5 ml), and  
25 passed through an SCX-2 column. The resultant colourless oil was purified using reverse phase chromatography, concentrated in vacuo, taken up in 5 M hydrochloric acid (10 ml),

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and heated to 90°C for 3 hours. This solution was freeze dried to give an oil (0.049g, 0.185 mmol). Resultant oil was passed through an SCX-2 column, dissolved in aqueous acetonitrile (c.a. 20 ml), and fumaric acid (0.0214g, 0.1850 mmol) added. After 5 minutes, this was freeze dried to give a white solid (0.070g, 0.185 mmol) as the title compound.  $\delta_H$  (300 MHz, MeOD) 7.47 (1H, t, Ar), 7.25 (1H, m, Ar), 7.13 (1H, t, Ar), 7.02 (1H, t, Ar), 6.70 (2H, s, fumarate), 3.21 (2H, s, NCH<sub>2</sub>Ar), 3.45 (2H, d, CH), 2.95 (2H, t, CH), 2.82 (1H, t, CH), 2.29 (2H, d, NCH<sub>2</sub>), 2.00 (2H, d, CH), 1.80 (2H, t, m), 1.68 (1H, t, CH), 0.85 (6H, d, CHMe<sub>2</sub>). LCMS 12 minute gradient, Rt = 1.99 mins, ( $M^+$ +1) = 265.2

10

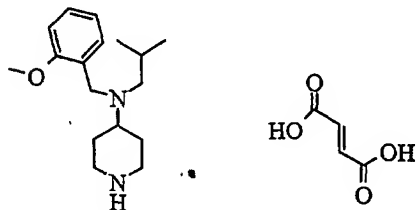
**EXAMPLE 44:****N-(2-methylpropyl)-N-[(2-chlorophenyl)methyl]piperidin-4-amine fumarate**

The title product was prepared similarly to Example 43 using 2-chlorobenzaldehyde.  $\delta_H$  (300 MHz, MeOD/ $CDCl_3$ ) 7.52 (1H, d, Ar), 7.30 (1H, d, Ar), 7.20 (2H, m, Ar), 6.75 (2H, s, fumarate), 3.75 (2H, s, NCH<sub>2</sub>Ar), 3.45 (2H, d, CH), 2.79 (2H, t, CH), 2.65 (1H, t, CH), 2.29 (2H, d, NCH<sub>2</sub>), 2.00 (2H, d, CH), 1.82 (2H, t, CH), 1.68 (1H, t, CH), 0.85 (6H, d, CHMe<sub>2</sub>). LCMS 12 minute gradient, Rt = 3.37 mins, ( $M^+$ +1) = 281.2/283.2

15

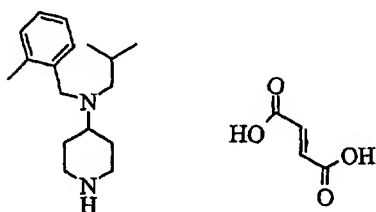
**EXAMPLE 45:****N-(2-methylpropyl)-N-[(2-methoxyphenyl)methyl]piperidin-4-amine fumarate**

20

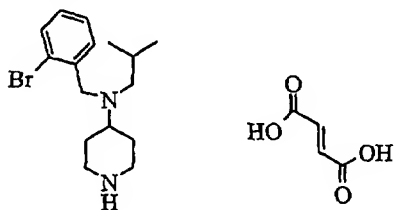


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The title product was prepared similarly to Example 43 using 2-methoxybenzaldehyde.  $\delta_H$  (300 MHz, MeOD) 7.30 (1H, d, Ar), 7.13 (1H, t, Ar), 6.83 (2H, m, Ar), 6.60 (2H, s, fumarate), 3.25 (3H, s, ArOMe), 3.25 (2H, s, NCH<sub>2</sub>Ar), 3.35 (2H, d, CH), 2.90-2.72 (3H, m, CH), 2.29 (2H, d, NCH<sub>2</sub>), 1.95 (2H, d, CH), 1.75 (2H, t, CH), 1.65 (1H, m, CH), 0.75  
5 (6H, d, CHMe<sub>2</sub>). LCMS 12 minute gradient, Rt = 1.21 mins, ( $M^+$ +1) = 277.3

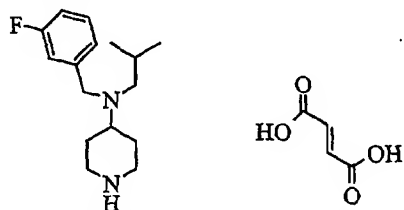
**EXAMPLE 46:****N-(2-methylpropyl)-N-[(2-methylphenyl)methyl]piperidin-4-amine fumarate**

The title product was prepared similarly to Example 43 using 2-methylbenzaldehyde.  $\delta_H$   
10 (300 MHz, MeOD/CDCl<sub>3</sub>) 7.18 (1H, m, Ar), 7.00 (3H, m, Ar), 6.58 (2H, s, fumarate), 3.48 (2H, s, NCH<sub>2</sub>Ar), 3.28 (2H, d, CH), 2.70-2.45 (3H, m, CH), 2.20 (3H, s, ArMe), 2.10 (2H, d, NCH<sub>2</sub>), 1.80 (2H, d, CH), 1.68 (2H, t, CH), 1.59 (1H, m, CH), 0.70 (6H, d, CHMe<sub>2</sub>). LCMS 12 minute gradient, Rt = 2.71 mins, ( $M^+$ +1) = 261.3

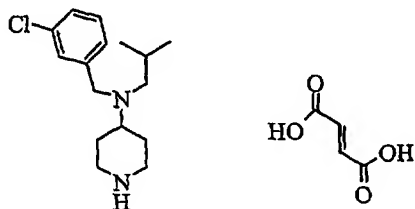
**EXAMPLE 47:****N-(2-methylpropyl)-N-[(2-bromophenyl)methyl]piperidin-4-amine fumarate**

The title product was prepared similarly to Example 43 using 2-bromobenzaldehyde.  $\delta_H$   
20 (300 MHz, MeOD/CDCl<sub>3</sub>) 7.55 (2H, t, Ar), 7.29 (1H, t, Ar), 7.10 (1H, t, Ar), 6.72 (2H, s, fumarate), 3.75 (2H, s, NCH<sub>2</sub>Ar), 3.42 (2H, d, CH), 2.80 (2H, t, CH), 2.65 (1H, t, CH), 2.27 (2H, d, NCH<sub>2</sub>), 2.00 (2H, d, CH), 1.82 (2H, t, CH), 1.68 (1H, m, CH), 0.89 (6H, d, CHMe<sub>2</sub>). LCMS 12 minute gradient, Rt = 3.85 mins, ( $M^+$ +1) = 323.1/325.1

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**EXAMPLE 48:****N-(2-methylpropyl)-N-[(3-fluorophenyl)methyl]piperidin-4-amine fumarate**

The title product was prepared similarly to Example 43 using 3-fluorobenzaldehyde.  $\delta_H$  (300 MHz, MeOD) 7.19 (1H, q, Ar), 7.05 (2H, t, Ar), 6.85 (1H, t, Ar), 6.60 (2H, s, fumarate), 3.58 (2H, s, NCH<sub>2</sub>Ar), 3.32 (2H, d, CH), 2.82 (2H, t, CH), 2.70 (1H, t, CH), 2.19 (2H, d, NCH<sub>2</sub>), 1.90 (2H, d, CH), 1.75-1.50 (3H, m, CH), 0.78 (6H, d, CHMe<sub>2</sub>). LCMS 12 minute gradient, Rt = 2.29 mins, ( $M^+$ +1) = 265.2

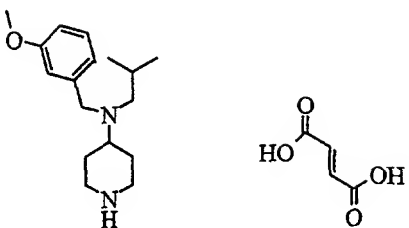
**EXAMPLE 49:****N-(2-methylpropyl)-N-[(3-chlorophenyl)methyl]piperidin-4-amine fumarate**

The title product was prepared similarly to Example 43 using 3-chlorobenzaldehyde.  $\delta_H$  (300 MHz, MeOD) 7.40 (1H, s, Ar), 7.30 (2H, m, Ar), 7.25 (1H, m, Ar), 6.72 (2H, s, fumarate), 3.68 (2H, s, NCH<sub>2</sub>Ar), 3.45 (2H, d, CH), 2.95 (2H, t, CH), 2.83 (1H, t, CH), 2.39 (2H, d, NCH<sub>2</sub>), 2.02 (2H, d, CH), 1.88-1.62 (3H, m, CH), 0.90 (6H, d, CHMe<sub>2</sub>). LCMS 12 minute gradient, Rt = 3.24 mins, ( $M^+$ +1) = 281.2/283.2

**EXAMPLE 50:****N-(2-methylpropyl)-N-[(3-methoxyphenyl)methyl]piperidin-4-amine fumarate**



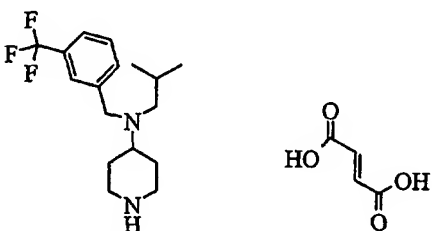
-73-



The title product was prepared similarly to Example 43 using 3-methoxybenzaldehyde.  $\delta_H$  (300 MHz, MeOD) 7.20 (1H, t, Ar), 6.95 (2H, m, Ar), 6.79 (1H, dd, Ar), 6.70 (2H, s, fumarate), 3.78 (3H, s, ArOMe), 3.65 (2H, s, NCH<sub>2</sub>Ar), 3.42 (2H, d, CH), 2.92 (2H, t, CH), 2.82 (1H, t, CH), 2.30 (2H, d, NCH<sub>2</sub>), 2.00 (2H, d, CH), 1.87-1.64 (3H, m, CH), 0.90 (6H, d, CHMe<sub>2</sub>). LCMS 12 minute gradient, Rt = 1.56 mins, ( $M^+$ +1) = 277.3

**EXAMPLE 51:**

**N-(2-methylpropyl)-N-([3-(trifluoromethyl)phenyl]methyl)piperidin-4-amine fumarate**

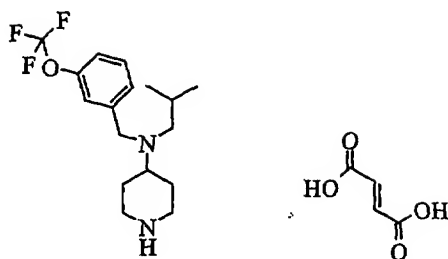


The title product was prepared similarly to Example 43 using 3-trifluoromethylbenzaldehyde.  $\delta_H$  (300 MHz, MeOD/CDCl<sub>3</sub>) 7.59 (1H, s, Ar), 7.51 (2H, m, Ar), 7.42 (1H, q, Ar), 6.68 (2H, s, fumarate), 3.65 (2H, s, NCH<sub>2</sub>Ar), 3.42 (2H, d, CH), 2.82-2.60 (3H, m, CH), 2.22 (2H, d, NCH<sub>2</sub>), 1.95 (2H, d, CH), 1.80 (2H, t, CH), 1.65 (1H, m, CH), 0.89 (6H, d, CHMe<sub>2</sub>). LCMS 12 minute gradient, Rt = 4.15 mins, ( $M^+$ +1) = 315.2

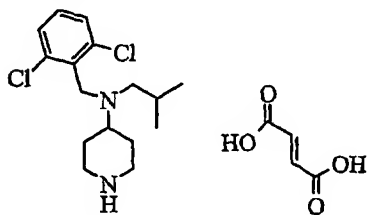
**EXAMPLE 52:**

**N-(2-methylpropyl)-N-([3-(trifluoromethoxy)phenyl]methyl)piperidin-4-amine fumarate**

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- The title product was prepared similarly to Example 43 using 3-trifluoromethoxybenzaldehyde.  $\delta_H$  (300 MHz, MeOD/ $CDCl_3$ ) 7.32 (1H, m, Ar), 7.22 (2H, m, Ar), 7.08 (1H, d, Ar), 6.80 (2H, s, fumarate), 3.68 (2H, s,  $NCH_2Ar$ ), 3.40 (2H, br, CH), 2.79 (2H, t, CH), 2.70 (1H, m, CH), 2.24 (2H, d,  $NCH_2$ ), 2.00-1.75 (4H, m, CH), 1.62 (1H, m, CH), 0.85 (6H, d,  $CHMe_2$ ). LCMS 12 minute gradient,  $R_t$  = 4.33 mins,  $(M^+ + 1) = 331.2$

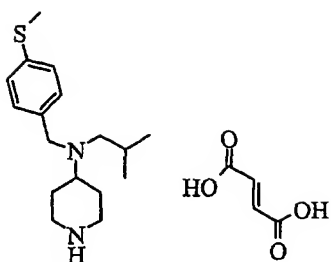
**EXAMPLE 53:****N-(2-methylpropyl)-N-[(2,6-dichlorophenyl)methyl]piperidin-4-amine fumarate**

- The title product was prepared similarly to Example 43 using 2,6-dichlorobenzaldehyde.  $\delta_H$  (300 MHz, MeOD) 7.28 (2H, m, Ar), 7.15 (1H, t, Ar), 6.59 (2H, s, fumarate), 3.85 (2H, s,  $NCH_2Ar$ ), 3.38 (2H, d, CH), 2.85 (2H, t, CH), 2.75 (1H, t, CH), 2.29 (2H, d,  $NCH_2$ ), 1.98 (2H, d, CH), 1.78 (2H, m, CH), 1.48 (1H, m, CH), 0.63 (6H, d,  $CHMe_2$ ). LCMS 12 minute gradient,  $R_t$  = 4.80 mins,  $(M^+ + 1) = 315.1/317.2$

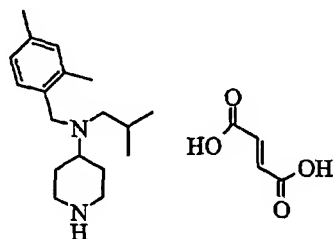
15

**EXAMPLE 54:****N-(2-methylpropyl)-N-[(4-methylthiophenyl)methyl]piperidin-4-amine fumarate**

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The title product was prepared from tert-butyl 4-isobutylamino-piperidine-1-carboxylate and 4-(methylthio)benzaldehyde using the method described in example 36. LCMS 12 mins gradient Rt = 2.83 ( $M^+ + 1$ ) 293.2. <sup>1</sup>H NMR (d<sub>6</sub>-DMSO)  $\delta$  = 7.25 (2H, d, J = 8.29 Hz), 7.20 (2H, d, J = 8.48 Hz), 6.42 (2H, s), 3.52 (2H, s), 3.25 (2H, brd), 2.81-2.59 (3H, m),  
 5 2.45 (3H, s, SMe), 2.16 (2H, d, J = 7.16 Hz), 1.78-1.57 (5H, m), 0.80 (6H, d, J = 6.6 Hz).

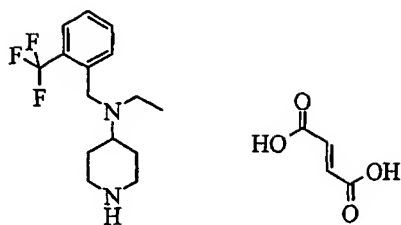
**EXAMPLE 55:****N-(2-methylpropyl)-N-[(2,4-dimethylphenyl)methyl]piperidin-4-amine fumarate**

The title product was prepared from tert-butyl 4-isobutylamino-piperidine-1-carboxylate and 2,4-dimethylbenzaldehyde using the method described in example 36. LCMS 12 mins gradient Rt = 3.408 ( $M^+ + 1$ ) 275.3. <sup>1</sup>H NMR (d<sub>6</sub>-DMSO)  $\delta$  = 7.17 (1H, d, J = 8.10 Hz), 6.93-6.91 (2H, m), 6.42 (2H, s), 3.51 (2H, s), 3.38 (2H, brd), 2.74-2.63 (4H, m), 2.51 (3H, s), 2.50 (3H, s), 2.24 (2H, d, J = 8.48 Hz), 1.79-1.66 (4H, m), 1.58-1.49 (1H, m),  
 10 0.75 (6H, d, J = 6.4 Hz).

15

**EXAMPLE 56:****N-ethyl-N-[[2-(trifluoromethyl)phenyl]methyl]piperidin-4-amine fumarate**

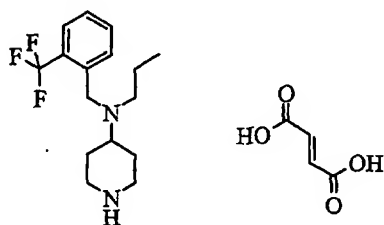
-76-



To a solution of 1,1-dimethylethyl 4-([2-(trifluoromethyl)phenyl]methyl)amino)piperidine-1-carboxylate (0.54 g, 1.5 mmol, 1 eq) in 1,2-dichloroethane (10 ml) was added a solution of sodium triacetoxyborohydride (0.95 g, 4.5 mmol, 3 eq) in dimethylformamide (2 ml) followed by a solution of acetaldehyde (132 mg, 4.5 mmol, 3 eq) in 1,2-dichloroethane (1 ml) and the mixture left to stir for 16 h. The reaction was quenched with water (10 ml) and the organic layer separated by passing through a hydrophobic frit. This was diluted with methanol (10 ml) and loaded onto a SCX-2 ion exchange cartridge (5 g) washed with methanol (15 ml) and the product eluted with 2M ammonia in methanol solution (15 ml). The solvent removed *in vacuo* to give 1,1-dimethylethyl 4-([2-(trifluoromethyl)phenyl]methyl)(ethyl)amino]-piperidine-1-carboxylate as a colourless oil. To this oil was added a solution of anisole (1.4 ml) and trifluoroacetic acid (1.4 ml, 18.3 mmol, 12 eq), in dichloromethane (7 ml) and the mixture stirred at room temperature for 16 h. The solvent removed *in vacuo* and the residue diluted with methanol (5 ml) and loaded onto SCX-2 ion exchange cartridge (5 g). The column was washed with methanol (15 ml) and eluting the product with 2M ammonia in methanol solution (15 ml) the solvent removed *in vacuo* to give (306 mg, 71%) as a colourless oil. The product was taken up in diethyl ether (15 ml) and a few drops of methanol to solubilize and a hot solution of fumaric acid (122 mg, 1.1 mmol, 1 eq) in methanol (1 ml) was added. The solution was heated and a few drops of methanol added until all solid was in solution, then the mixture was allowed to slowly cool to 0°C. The product was collected by filtration and dried in a vacuum oven (40°C for 2 h) to give N-ethyl-N-([2-(trifluoromethyl)phenyl]methyl)piperidin-4-amine fumarate (247 mg, 41%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 7.98 (1H, d,  $J = 7.7$  Hz, ArH), 7.67-7.58 (2H, m, ArH), 7.42-7.37 (1H, m, ArH), 6.70 (2H, s, fumarate CH), 3.88 (2H, s, CH<sub>2</sub>Ar), 3.47-3.43 (2H, m, NCH<sub>2</sub>), 3.02-2.87 (3H, m, NCH, NCH<sub>2</sub>), 2.65 (2H, q,  $J = 7.1$  Hz, CH<sub>2</sub>), 2.08-2.02

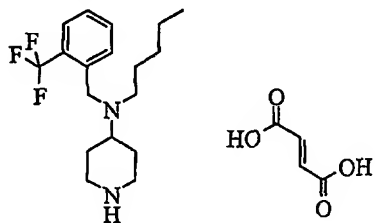
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(2H, m, CCH<sub>2</sub>), 1.86-1.72 (2H, m, CCH<sub>2</sub>) and 1.05 (3H, t, J = 7.1 Hz, CH<sub>3</sub>); LCMS 12 min, Rt = 2.16 min, (M<sup>+</sup>+1) = 287.2.

**EXAMPLE 57:**5 **N-propyl-N-{[2-(trifluoromethyl)phenyl]methyl}piperidin-4-amine fumarate**

As example 56 with 1,1-dimethylethyl 4-([2-(trifluoromethyl)phenyl]methyl)amino)piperidine-1-carboxylate and propionaldehyde to give N-propyl-N-{[2-(trifluoromethyl)phenyl]methyl}piperidin-4-amine fumarate (223 mg, 36%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 7.96 (1H, d, J = 7.7 Hz, ArH), 7.67-7.58 (2H, m, ArH), 7.42-7.38 (1H, m, ArH), 6.70 (2H, s, fumarate CH), 3.88 (2H, s, CH<sub>2</sub>Ar), 3.47-3.43 (2H, m, NCH<sub>2</sub>), 3.01-2.82 (3H, m, NCH, NCH<sub>2</sub>), 2.54 (2H, t, J = 7.3 Hz, CH<sub>2</sub>), 2.07-2.02 (2H, m, CCH<sub>2</sub>), 1.86-1.72 (2H, m, CCH<sub>2</sub>), 1.46 (2H, septet, J = 7.3 Hz, CH<sub>2</sub>) and 0.89 (3H, t, J = 7.3 Hz, CH<sub>3</sub>); LCMS 12 min, Rt = 3.62 min, (M<sup>+</sup>+1) = 301.2.

15

**EXAMPLE 58:**20 **N-pentyl-N-{[2-(trifluoromethyl)phenyl]methyl}piperidin-4-amine fumarate**

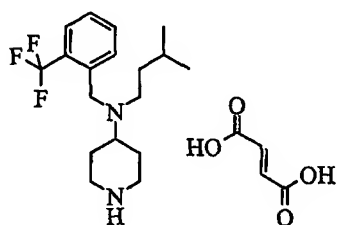
As example 56 with 1,1-dimethylethyl 4-([2-(trifluoromethyl)phenyl]methyl)amino)piperidine-1-carboxylate and valeraldehyde to give N-pentyl-N-{[2-(trifluoromethyl)phenyl]methyl}piperidin-4-amine fumarate (236 mg, 35%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 7.95 (1H, d, J = 7.9 Hz, ArH), 7.67-

-78-

7.58 (2H, m, ArH), 7.43-7.39 (1H, m, ArH), 6.70 (2H, s, fumarate CH), 3.87 (2H, s, CH<sub>2</sub>Ar), 3.47-3.43 (2H, m, NCH<sub>2</sub>), 3.01-2.84 (3H, m, NCH, NCH<sub>2</sub>), 2.57 (2H, t, J = 7.2 Hz, CH<sub>2</sub>), 2.07-2.03 (2H, m, CCH<sub>2</sub>), 1.86-1.71 (2H, m, CCH<sub>2</sub>), 1.44-1.42 (2H, m, CH<sub>2</sub>), 1.29-1.17 (4H, m, CH<sub>2</sub>) and 0.90-0.86 (3H, m, CH<sub>3</sub>); LCMS 12 min, Rt = 5.01 min, (M<sup>+</sup>+1) = 329.2.

**EXAMPLE 59:**

**N-(3-methylbutyl)-N-[[2-(trifluoromethyl)phenyl]methyl]piperidin-4-amine fumarate**

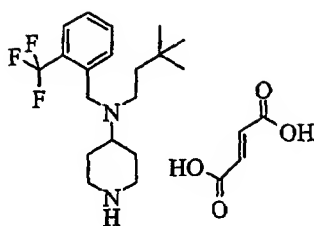


As example 56 with 1,1-dimethylethyl 4-([2-(trifluoromethyl)phenyl]methyl)amino)piperidine-1-carboxylate and 3-methylbutyraldehyde to give N-(3-methylbutyl)-N-[[2-(trifluoromethyl)phenyl]methyl]piperidin-4-amine fumarate (348 mg, 52%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 7.94 (1H, d, J = 7.9, ArH), 7.67-7.58 (2H, m, ArH), 7.43-7.38 (1H, m, ArH), 6.70 (2H, s, fumarate CH), 3.87 (2H, s, CH<sub>2</sub>Ar), 3.48-3.44 (2H, m, NCH<sub>2</sub>), 3.01-2.85 (3H, m, NCH, NCH<sub>2</sub>), 2.59 (2H, t, J = 7.5 Hz, NCH<sub>2</sub>), 2.07-2.03 (2H, m, CCH<sub>2</sub>), 1.87-1.73 (2H, m, CCH<sub>2</sub>), 1.65-1.53 (1H, m, CH(CH<sub>3</sub>)<sub>2</sub>), 1.37-1.30 (2H, m, CH<sub>2</sub>) and 0.84 (6H, d, J = 6.6 Hz, CH<sub>3</sub>); LCMS 12 min, Rt = 4.87 min, (M<sup>+</sup>+1) = 329.2.

**EXAMPLE 60:**

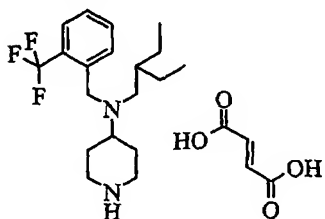
**N-(3,3-dimethylbutyl)-N-[[2-(trifluoromethyl)phenyl]methyl]piperidin-4-amine fumarate**

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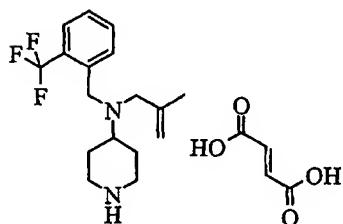
As example 56 with 1,1-dimethylethyl 4-({[2-(trifluoromethyl)phenyl]methyl}amino)piperidine-1-carboxylate and 3,3-dimethylbutyraldehyde to give N-(3,3-dimethylbutyl)-N-{[2-(trifluoromethyl)phenyl]methyl}piperidin-4-amine fumarate (102 mg, 15%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 7.95 (1H, d,  $J = 7.7$ , ArH), 7.67-7.58 (2H, m, ArH), 7.42-7.38 (1H, m, ArH), 6.70 (2H, s, fumarate CH), 3.87 (2H, s,  $CH_2Ar$ ), 3.47-3.44 (2H, m,  $NCH_2$ ), 3.02-2.86 (3H, m, NCH,  $NCH_2$ ), 2.63-2.57 (2H, m,  $NCH_2$ ), 2.08-2.03 (2H, m,  $CCH_2$ ), 1.87-1.73 (2H, m,  $CCH_2$ ), 1.41-1.36 (2H, m,  $CH_2$ ), and 0.86 (9H, s,  $CH_3$ ); LCMS 12 min,  $R_t = 5.35$  min,  $(M^+ + 1) = 343.2$ .

10

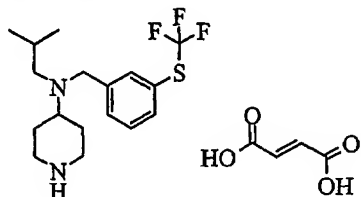
**EXAMPLE 61:****N-(2-ethylbutyl)-N-{[2-(trifluoromethyl)phenyl]methyl}piperidin-4-amine fumarate**

As example 56 with 1,1-dimethylethyl 4-({[2-(trifluoromethyl)phenyl]methyl}amino)piperidine-1-carboxylate and 2-ethylbutyraldehyde to give N-(2-ethylbutyl)-N-{[2-(trifluoromethyl)phenyl]methyl}piperidin-4-amine fumarate (302 mg, 44%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 7.93 (1H, d,  $J = 7.9$ , ArH), 7.67-7.58 (2H, m, ArH), 7.43-7.38 (1H, m, ArH), 6.70 (2H, s, fumarate CH), 3.86 (2H, s,  $CH_2Ar$ ), 3.47-3.43 (2H, m,  $NCH_2$ ), 2.98-2.78 (3H, m, NCH,  $NCH_2$ ), 2.42 (2H, d,  $J = 6.2$  Hz,  $NCH_2$ ), 2.07-2.03 (2H, m,  $CCH_2$ ), 1.86-1.72 (2H, m,  $CCH_2$ ), 1.46-1.27 (5H, m,  $CH_2$ , CH), and 0.82 (6H, t,  $J = 7.2$ ,  $CH_3$ ); LCMS 12 min,  $R_t = 6.57$  min,  $(M^+ + 1) = 343.3$ .

20

**EXAMPLE 62:****N-(2-methylprop-2-enyl)-N-{[2-(trifluoromethyl)phenyl]methyl}piperidin-4-amine fumarate**

5 As example 56 with 1,1-dimethylethyl 4-([2-(trifluoromethyl)phenyl]methyl)amino)piperidine-1-carboxylate and methacrolein to give N-(2-methylprop-2-enyl)-N-{[2-(trifluoromethyl)phenyl]methyl}piperidin-4-amine fumarate (224 mg, 35%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 7.95 (1H, d,  $J = 7.7$ , ArH), 7.67-7.59 (2H, m, ArH), 7.44-7.39 (1H, m, ArH), 6.70 (2H, s, fumarate CH), 4.99  
 10 (2H, s, CCH<sub>2</sub>), 3.84 (2H, s, CH<sub>2</sub>Ar), 3.48-3.44 (2H, m, NCH<sub>2</sub>), 3.10 (2H, s, CH<sub>2</sub>), 2.98-2.81 (3H, m, NCH, NCH<sub>2</sub>), 2.09-2.04 (2H, m, CCH<sub>2</sub>), 1.90-1.80 (2H, m, CCH<sub>2</sub>), 1.77 (3H, s, CH<sub>3</sub>); LCMS 12 min, Rt = 5.71 min, ( $M^+ + 1$ ) = 313.2.

**EXAMPLE 63:****N-(2-methylpropyl)-N-{[3-(trifluoromethylthio)phenyl]methyl}piperidin-4-amine fumarate**

The procedure for reductive amination in example 36 applies for this compound using 3-(trifluoromethylthio)benzaldehyde. The N-Boc deprotection procedure was as follows: The boc-amine (0.65mg, 1.46mmol) was dissolved in dichloromethane (5ml), and  
 20 trifluoroacetic acid (2ml) and anisole (2ml) were added in one portion, under an atmosphere of nitrogen. The reaction was monitored by thin layer chromatography (100% ethyl acetate; reactant. r.f. 0.4, product r.f. 0.0). After 2 hours, the reaction was

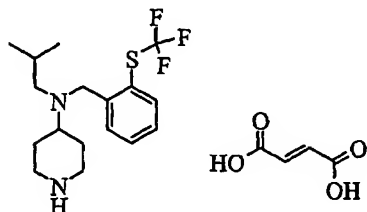


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concentrated *in vacuo*, azeotroped with dichloromethane (c.a. 25ml), taken up in methanol (c.a. 5ml) and passed through an SCX-2 column. The resultant colourless oil was purified by preparative HPLC using the UV-Flex system. The resulting colourless oil was dissolved in aqueous acetonitrile (c.a. 20ml), and fumaric acid (1eq) added. After 5 minutes, this was freeze dried to give a white solid (0.448g, 0.96mmol) as the title compound.  $\delta_H$  (300 MHz, MeOD) 7.65 (1H, m), 7.52 (2H, m), 7.35 (1H, m), 6.55 (2H, s, fumarate), 3.65 (2H, s), 3.40 (2H, m), 2.81 (3H, m), 2.25 (2H, d), 1.95 (2H, m), 1.72 (3H, m), 0.79 (6H, d). LCMS 12 minute gradient,  $R_t$  = 4.74 mins,  $(M^+ + 1) = 347.2$

#### 10 EXAMPLE 64:

N-(2-methylpropyl)-N-([2-(trifluoromethylthio)phenyl]methyl)piperidin-4-amine fumarate

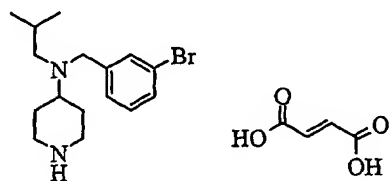


The compound was prepared similarly to example 63 using 4-isobutylamino-piperidine-1-carboxylic acid *tert*-butyl ester (0.40g, 1.56mmol) and 2-(trifluoromethylthio)benzaldehyde (0.90, 4.67mmol) to give the title compound as a white solid (0.58g, 1.25mmol).  $\delta_H$  (300 MHz, MeOD) 7.67 (2H, m), 7.52 (1H, t), 7.35 (1H, m), 6.65 (2H, s, fumarate), 3.95 (2H, s), 3.50 (2H, m), 2.90 (3H, m), 2.27 (2H, d), 2.10 (2H, m), 1.87 (2H, m), 1.57 (1H, m), 0.79 (6H, d). LCMS 12 minute gradient,  $R_t$  = 5.81 mins,  $(M^+ + 1) = 347.2$

20

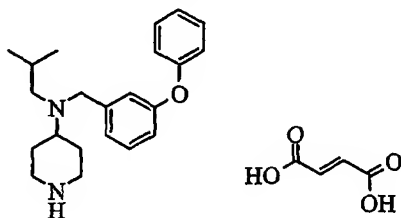
#### EXAMPLE 65:

N-(2-methylpropyl)-N-[(3-bromophenyl)methyl]piperidin-4-amine fumarate

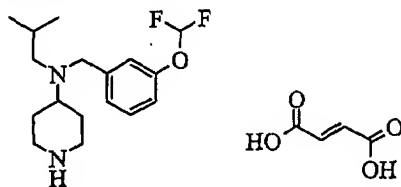


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The compound was prepared similarly to example 63 using 4-isobutylamino-piperidine-1-carboxylic acid *tert*-butyl ester (0.40g, 1.56mmol) and 3-bromobenzaldehyde (0.86, 4.67mmol) to give the title compound as an off-white solid (0.71g, 1.59mmol).  $\delta_H$  (300 MHz, MeOD) 7.57 (1H, s), 7.35 (2H, m), 7.24 (1H, m), 6.58 (2H, s, fumarate), 3.67 (2H, s), 3.45 (2H, m), 2.96 (2H, m), 2.83 (1H, m), 2.30 (2H, d), 2.00 (2H, m), 1.75 (3H, m), 0.87 (6H, d). LCMS 12 minute gradient,  $R_t$  = 3.62 mins,  $(M^+ + 1) = 326.1$

**EXAMPLE 66:****N-(2-methylpropyl)-N-[(3-phenoxyphenyl)methyl]piperidin-4-amine fumarate**

The compound was prepared similarly to example 63 using 4-isobutylamino-piperidine-1-carboxylic acid *tert*-butyl ester (0.40g, 1.56mmol) and 3-phenoxybenzaldehyde (0.93g, 4.67mmol) to give the title compound as a white solid (0.53g, 1.16mmol).  $\delta_H$  (300 MHz, MeOD) 7.32 (3H, m), 7.12 (2H, m), 6.97 (3H, m), 6.88 (1H, m), 6.70 (2H, s, fumarate), 3.66 (2H, s), 3.40 (2H, m), 2.85 (3H, m), 2.26 (2H, d), 1.92 (2H, m), 1.69 (3H, m), 0.82 (6H, d). LCMS 12 minute gradient,  $R_t$  = 4.21 mins,  $(M^+ + 1) = 339.3$

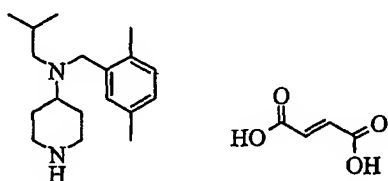
**EXAMPLE 67:****N-(2-methylpropyl)-N-[[3-(difluoromethoxy)phenyl]methyl]piperidin-4-amine fumarate**

The compound was prepared similarly to example 63 using 4-isobutylamino-piperidine-1-carboxylic acid *tert*-butyl ester (0.40g, 1.56mmol) and 3-(difluoromethoxy)benzaldehyde (0.80g, 4.67mmol) to give the title compound as a white solid (0.53g, 1.23mmol).  $\delta_H$

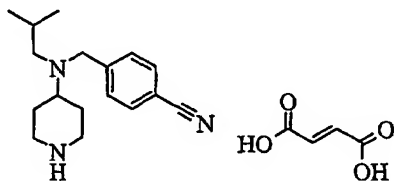
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(300 MHz, MeOD) 7.32 (1H, m), 7.23 (2H, m), 7.05 (1H, m), 6.78-6.53 (1H, br-t,  $\text{CHF}_2$ ), 6.68 (2H, s, fumarate), 3.69 (2H, s), 3.42 (2H, m), 2.86 (3H, m), 2.30 (2H, d), 2.00 (2H, m), 1.75 (3H, m), 0.89 (6H, d). LCMS 12 minute gradient,  $R_t = 3.23$  mins,  $(M^+ + 1) = 313.2$

5

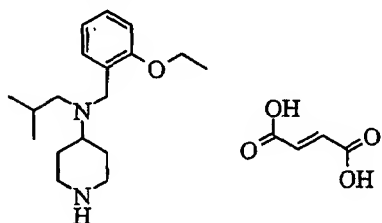
**EXAMPLE 68:****N-(2-methylpropyl)-N-[(2,5-dimethylphenyl)methyl]piperidin-4-amine fumarate**

The compound was prepared similarly to example 63 using 4-isobutylamino-piperidine-1-carboxylic acid *tert*-butyl ester (0.40g, 1.56mmol) and 2,5-dimethylbenzaldehyde (0.76g, 4.67mmol) to give the title compound as a white solid (0.50g, 1.28mmol).  $\delta_H$  (300 MHz, MeOD) 7.14 (1H, s), 6.97 (2H, m), 6.69 (2H, s, fumarate), 3.63 (2H, s), 3.42 (2H, m), 2.85 (3H, m), 2.32 (3H, s), 2.29 (3H, s), 2.28 (2H, d), 2.03 (2H, m), 1.85 (2H, m), 1.60 (1H, m), 0.83 (6H, d). LCMS 12 minute gradient,  $R_t = 3.20$  mins,  $(M^+ + 1) = 275.3$

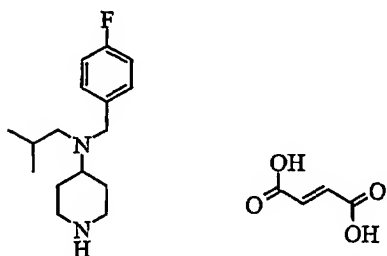
15 **EXAMPLE 69:****N-(2-methylpropyl)-N-[(4-cyanophenyl)methyl]piperidin-4-amine fumarate**

The compound was prepared similarly to example 63 using 4-isobutylamino-piperidine-1-carboxylic acid *tert*-butyl ester (0.50g, 1.95mmol) and 4-cyanobenzaldehyde (0.76g, 5.85mmol) to give the title compound as a white solid (0.45g, 1.16mmol).  $\delta_H$  (300 MHz, MeOD) 7.92 (2H, d), 7.78 (2H, d), 6.91 (2H, s, fumarate), 3.97 (2H, s), 3.65 (2H, m), 3.08 (3H, m), 2.52 (2H, d), 2.24 (2H, m), 1.95 (3H, m), 1.08 (6H, d). LCMS 12 minute gradient,  $R_t = 2.93$  mins,  $(M^+ + 1) = 272.2$

20

**EXAMPLE 70:****N-(2-methylpropyl)-N-[(2-ethoxyphenyl)methyl]piperidin-4-amine fumarate**

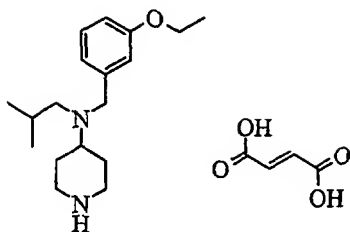
The compound was prepared similarly to example 63 using 4-isobutylamino-piperidine-1-carboxylic acid *tert*-butyl ester (0.40g, 1.56mmol) and 2-ethoxybenzaldehyde (0.70g, 4.68mmol) to give the title compound as a white solid (0.52g, 1.28mmol).  $\delta_H$  (300 MHz, MeOD) 7.38 (1H, m), 7.17 (1H, m), 6.89 (2H, m), 6.66 (2H, s, fumarate), 4.05 (2H, q), 3.72 (2H, s), 3.43 (2H, m), 2.87 (3H, m), 2.32 (2H, d), 2.02 (2H, m), 1.76 (3H, m), 1.40 (3H, t), 0.85 (6H, d). LCMS 12 minute gradient,  $R_t$  = 2.03 mins,  $(M^+ + 1) = 291.3$

**EXAMPLE 71:****N-(2-methylpropyl)-N-[(4-fluorophenyl)methyl]piperidin-4-amine fumarate**

The compound was prepared similarly to example 63 using 4-isobutylamino-piperidine-1-carboxylic acid *tert*-butyl ester (0.40g, 1.56mmol) and 4-fluorobenzaldehyde (0.69g, 4.68mmol) to give the title compound as a white solid (0.41g, 1.05mmol).  $\delta_H$  (300 MHz, MeOD) 7.35 (2H, m), 7.05 (2H, m), 6.67 (2H, s, fumarate), 3.62 (2H, s), 3.41 (2H, m), 2.82 (3H, m), 2.23 (2H, d), 1.96 (2H, m), 1.70 (3H, m), 0.83 (6H, d). LCMS 12 minute gradient,  $R_t$  = 1.79 mins,  $(M^+ + 1) = 265.2$

**EXAMPLE 72:****N-(2-methylpropyl)-N-[(3-ethoxyphenyl)methyl]piperidin-4-amine fumarate**

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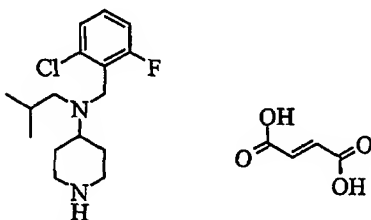


The compound was prepared similarly to example 63 using 4-isobutylamino-piperidine-1-carboxylic acid *tert*-butyl ester (0.40g, 1.56mmol) and 3-ethoxybenzaldehyde (0.69g, 4.68mmol) to give the title compound as a white solid (0.31g, 0.74mmol).  $\delta_H$  (300 MHz, MeOD) 7.16 (1H, m), 6.91 (2H, m), 6.74 (1H, m), 6.71 (2H, s, fumarate), 4.05 (2H, q), 3.64 (2H, s), 3.41 (2H, m), 2.86 (3H, m), 2.28 (2H, d), 1.97 (2H, m), 1.72 (3H, m), 1.36 (3H, t), 0.86 (6H, d). LCMS 12 minute gradient, Rt = 2.77 mins, ( $M^+ + 1$ ) = 291.3

**EXAMPLE 73:**

**N-(2-methylpropyl)-N-[(2-chloro-6-fluorophenyl)methyl]piperidin-4-amine**

10 **fumarate**

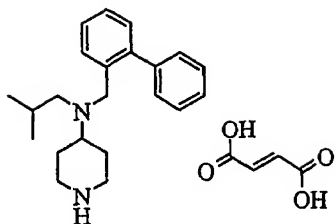


The compound was prepared similarly to example 63 using 4-isobutylamino-piperidine-1-carboxylic acid *tert*-butyl ester (0.40g, 1.56mmol) and 2-chloro-6-fluorobenzaldehyde (0.74g, 4.67mmol) to give the title compound as a white solid (0.42g, 1.01mmol).  $\delta_H$  (300 MHz, MeOD) 7.26 (2H, m), 7.06 (1H, m), 6.65 (2H, s, fumarate), 3.79 (2H, s), 3.44 (2H, m), 2.82 (2H, dt), 2.78 (1H, m), 2.25 (2H, d), 2.04 (2H, m), 1.81 (2H, m), 1.62 (1H, m), 0.74 (6H, d). LCMS 12 minute gradient, Rt = 3.96 mins, ( $M^+ + 1$ ) = 299.2

**EXAMPLE 74:**

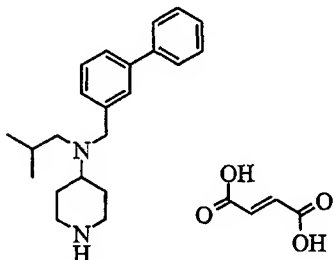
**N-(2-methylpropyl)-N-[(2-biphenyl)methyl]piperidin-4-amine fumarate**

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- (i) The N-(2-methylpropyl)-N-[(2-bromophenyl)methyl]4-piperidin-1-amine carboxylic acid tert-butyl ester was prepared similarly to example 63 using 4-isobutylamino-piperidine-1-carboxylic acid *tert*-butyl ester (0.40g, 1.56mmol) and 2-bromobenzaldehyde (0.86g, 4.67mmol) to give a yellow oil (0.54g, 1.27mmol). LCMS 5 12 minute gradient,  $R_t = 3.58$  mins,  $(M^+ + 1) = 426.2$
- (ii) N-(2-methylpropyl)-N-[(2-bromophenyl)methyl]4-piperidin-1-amine carboxylic acid tert-butyl ester (0.85g, 2.00mmol) in tetrahydrofuran (50ml) and water (50ml) was added phenyl boronic acid, bis(triphenylphosphine)palladium (II) chloride (0.14g, 0.20mmol) and sodium carbonate (0.42g, 4.00mmol), under an atmosphere of nitrogen. The mixture 10 was heated to 90°C and stirred for 3 h. The mixture was cooled, poured into diethyl ether (200ml) and washed with 2M NaOH (50ml). The organic was further washed with brine (50ml), dried ( $MgSO_4$ ) and concentrated in vacuo to a yellow oil. The oil was taken up in methanol (c.a. 5ml), and passed through an SCX-2 column to give a colourless oil (0.71g, 1.68mmol). The colourless oil (0.71g, 1.68mmol) was dissolved in dichloromethane 15 (5ml), and trifluoroacetic acid (2ml) and anisole (2ml) were added in portion, under an atmosphere of nitrogen. The reaction was monitored by thin layer chromatography (100% ethyl acetate; reactant r.f. 0.45, product r.f. 0.0). After 2 hours, the reaction was concentrated in vacuo, azeotroped with dichloromethane (c.a. 25ml), taken up in methanol (c.a. 5ml), and passed through an SCX-2 column. The resultant colourless oil 20 was purified by preparative HPLC using the UV-Flex system. The colourless oil was dissolved in aqueous acetonitrile (c.a. 20ml), and fumaric acid (1eq) added. After 5 minutes, this was freeze dried to give a white solid (0.73g, 0.66 mmol) as the title compound.  $\delta_H$  (300 MHz, MeOD) 7.48 (1H, m), 7.34-7.17 (7H, m), 7.05 (1H, m), 6.58 (2H, s, fumarate), 3.50 (2H, s), 3.21 (2H, m), 2.67 (2H, dt), 2.48 (1H, m), 2.02 (2H, d), 25 1.46 (5H, m), 0.58 (6H, d). LCMS 12 minute gradient,  $R_t = 4.09$  mins,  $(M^+ + 1) = 323.3$

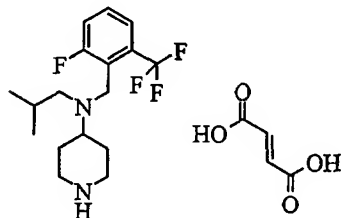
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**EXAMPLE 75:****N-(2-methylpropyl)-N-[(3-biphenyl)methyl]piperidin-4-amine fumarate**

(i) N-(2-methylpropyl)-N-[(3-bromophenyl)methyl]4-piperidine-1-carboxylic acid tert-butyl ester was prepared similarly to example 63 using 4-isobutylamino-piperidine-1-carboxylic acid *tert*-butyl ester (0.40g, 1.56mmol) and 3-bromobenzaldehyde (0.86g, 4.67mmol) to give the title compound as a pale yellow oil (0.55g, 1.27mmol). LCMS 12 minute gradient,  $R_t = 3.29$  mins,  $(M^+ + 1) = 426.2$ .

(ii) The compound was prepared similarly to example 74 using N-(2-methylpropyl)-N-[(3-bromophenyl)methyl]4-piperidine-1-carboxylic acid *tert*-butyl ester (0.66, 1.56mmol) and phenyl boronic acid (0.38g, 3.14mmol) to give the title compound as a white solid (0.44g, 1.00mmol).  $\delta_H$  (300 MHz, MeOD) 7.62 (3H, m), 7.51-7.30 (6H, m), 7.05 (1H, m), 6.71 (2H, s, fumarate), 3.75 (2H, s), 3.42 (2H, m), 2.89 (3H, m), 2.33 (2H, d), 2.06 (2H, m), 1.78 (3H, m), 0.91 (6H, d). LCMS 12 minute gradient,  $R_t = 4.05$  mins,  $(M^+ + 1) = 323.3$

15

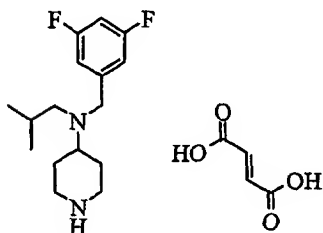
**EXAMPLE 76:****N-(2-methylpropyl)-N-[(2-fluoro-6-(trifluoromethyl)phenyl)methyl]piperidin-4-amine fumarate**

As example 26 with 1,1-dimethylethyl N-[(2-methylpropyl)amino]piperidine-1-carboxylate and 2-fluoro-6-(trifluoromethyl)benzaldehyde, further purified by MS

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guided preparative LC and loaded onto SCX-2 ion exchange cartridge (5 g). The column was washed with methanol (10 ml) and eluting the product with 2M ammonia in methanol solution (10 ml) the solvent removed *in vacuo* to give (117 mg, 23%) as a colourless oil. The product was taken up in diethyl ether (10 ml) and a few drops of methanol to solubilize and a hot solution of fumaric acid (41 mg, 0.3 mmol, 1 eq) in methanol (0.5 ml) was added. The solution was heated and a few drops of methanol added until all solid was in solution, then the mixture was allowed to slowly cool to 0°C. The product was collected by filtration and dried in a vacuum oven (40°C for 2 h) to give N-(2-methylpropyl)-N-[[2-fluoro-6-(trifluoromethyl)phenyl]methyl]piperidin-4-amine fumarate (121 mg, 18%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 7.57-7.48 (2H, m, ArH), 7.42-7.36 (1H, m, ArH), 6.70 (2H, s, fumarate CH), 3.89 (2H, s, CH<sub>2</sub>Ar), 3.50-3.45 (2H, m, NCH<sub>2</sub>), 3.00-2.90 (2H, m, NCH<sub>2</sub>), 2.87-2.77 (1H, m, NCH), 2.26 (2H, d, J = 7.2 Hz, NCH<sub>2</sub>), 2.04-2.00 (2H, m, CCH<sub>2</sub>), 1.91-1.77 (2H, m, CCH<sub>2</sub>) 1.59-1.48 (1H, m, CH(CH<sub>3</sub>)<sub>2</sub>) and 0.74 (6H, d, J = 6.6 Hz, CH<sub>3</sub>); LCMS 12 min, Rt = 5.55 min, (M<sup>+</sup>+1) = 333.2.

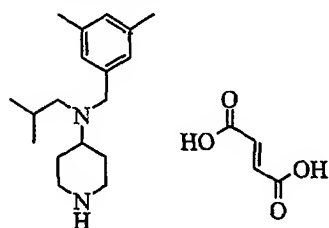
**EXAMPLE 77:****N-(2-methylpropyl)-N-[(3,5-difluorophenyl)methyl]piperidin-4-amine fumarate**

As example 56 with 1,1-dimethylethyl 4-[(2-methylpropyl)amino]piperidine-1-carboxylate and 3,5-difluorobenzaldehyde to give N-(2-methylpropyl)-N-[(3,5-difluorophenyl)methyl]piperidin-4-amine fumarate (264 mg, 44%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 7.01-6.98 (2H, m, ArH), 6.83-6.76 (1H, m, ArH), 6.70 (2H, s, fumarate CH), 3.69 (2H, s, CH<sub>2</sub>Ar), 3.47-3.43 (2H, m, NCH<sub>2</sub>), 3.00-2.90 (2H, m, NCH<sub>2</sub>), 2.87-3.76 (1H, m, NCH), 2.30 (2H, d, J = 7.2 Hz, NCH<sub>2</sub>), 2.04-2.00 (2H, m, CCH<sub>2</sub>), 1.84-

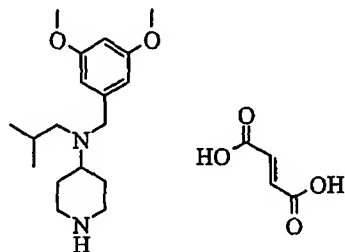


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1.66 (3H, m,  $\text{CH}(\text{CH}_3)_2$  and  $\text{CCH}_2$ ) and 0.91 (6H, d,  $J = 6.6$  Hz,  $\text{CH}_3$ ); LCMS 12 min,  $R_t = 4.15$  min,  $(M^+ + 1) = 283.2$ .

**EXAMPLE 78:**5 **N-(2-methylpropyl)-N-[(3,5-dimethylphenyl)methyl]piperidin-4-amine fumarate**

As example 56 with 1,1-dimethylethyl 4-[(2-methylpropyl)amino]piperidine-1-carboxylate and 3,5-dimethylbenzaldehyde to give N-(2-methylpropyl)-N-[(3,5-dimethylphenyl)methyl]piperidin-4-amine fumarate (356 mg, 61%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 6.97 (2H, s, ArH), 6.88 (1H, s, ArH), 6.70 (2H, s, fumarate CH), 3.61 (2H, s,  $\text{CH}_2\text{Ar}$ ), 3.45-3.41 (2H, m,  $\text{NCH}_2$ ), 2.96-2.79 (3H, m,  $\text{NCH}_2$  and  $\text{NCH}$ ), 2.30-2.29 (8H, m, Hz,  $\text{NCH}_2$  and  $\text{CH}_3$ ), 2.01-1.97 (2H, m,  $\text{CCH}_2$ ), 1.84-1.67 (3H, m,  $\text{CH}(\text{CH}_3)_2$  and  $\text{CCH}_2$ ) and 0.89 (6H, d,  $J = 6.6$  Hz,  $\text{CH}_3$ ); LCMS 12 min,  $R_t = 3.08$  min,  $(M^+ + 1) = 275.3$ .

**EXAMPLE 79:**15 **N-(2-methylpropyl)-N-[(3,5-dimethoxyphenyl)methyl]piperidin-4-amine fumarate**

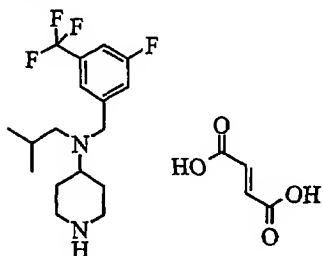
As example 56 with 1,1-dimethylethyl 4-[(2-methylpropyl)amino]piperidine-1-carboxylate and 3,5-dimethoxybenzaldehyde to give N-(2-methylpropyl)-N-[(3,5-dimethoxyphenyl)methyl]piperidin-4-amine fumarate (378 mg, 53%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 6.70 (2H, s, fumarate CH), 6.57-6.56 (2H, m, ArH), 6.36-6.35 (1H, m, ArH), 3.77 (6H, s,  $\text{OCH}_3$ ), 3.62 (2H, s,  $\text{CH}_2\text{Ar}$ ) 3.46-3.41 (2H, m,  $\text{NCH}_2$ ), 2.97-2.78 (3H, m,  $\text{NCH}_2$  and  $\text{NCH}$ ), 2.30 (2H, d,  $J = 7.2$  Hz,  $\text{NCH}_2$ ), 2.02-1.98 (2H, m,  $\text{CCH}_2$ ),

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1.84-1.68 (3H, m,  $\text{CH}(\text{CH}_3)_2$  and  $\text{CCH}_2$ ) and 0.92 (6H, d,  $J = 6.6$  Hz,  $\text{CH}_3$ ); LCMS 12 min,  $R_t = 2.66$  min,  $(M^+ + 1) = 307.2$ .

**EXAMPLE 80:**

5 **N-(2-methylpropyl)-N-[[3-fluoro-5-(trifluoromethyl)phenyl]methyl]piperidin-4-amine fumarate**

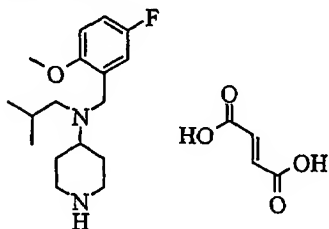


As example 56 with 1,1-dimethylethyl 4-[(2-methylpropyl)amino]piperidine-1-carboxylate and 3-fluoro-5-(trifluoromethyl)benzaldehyde to give N-(2-methylpropyl)-N-[[3-fluoro-5-(trifluoromethyl)phenyl]methyl]piperidin-4-amine fumarate (397 mg, 59%)  
 10 as a white solid.  $\delta_H$  (300 MHz, MeOD) 7.56 (1H, s, ArH), 7.43 (1H, d,  $J = 9.4$  Hz, ArH), 7.31 (1H, d,  $J = 8.5$  Hz, ArH), 6.70 (2H, s, fumarate CH), 3.77 (2H, s,  $\text{CH}_2\text{Ar}$ ), 3.48-3.44 (2H, m,  $\text{NCH}_2$ ), 3.01-2.79 (3H, m,  $\text{NCH}_2$  and  $\text{NCH}$ ), 2.32 (2H, d,  $J = 7.2$  Hz,  $\text{NCH}_2$ ), 2.06-2.02 (2H, m,  $\text{CCH}_2$ ), 1.86-1.63 (3H, m,  $\text{CH}(\text{CH}_3)_2$  and  $\text{CCH}_2$ ) and 0.89 (6H, d,  $J = 6.6$  Hz,  $\text{CH}_3$ ); LCMS 12 min,  $R_t = 5.61$  min,  $(M^+ + 1) = 333.2$ .

15

**EXAMPLE 81:**

**N-(2-methylpropyl)-N-[(5-fluoro-2-methoxyphenyl)methyl]piperidin-4-amine fumarate**



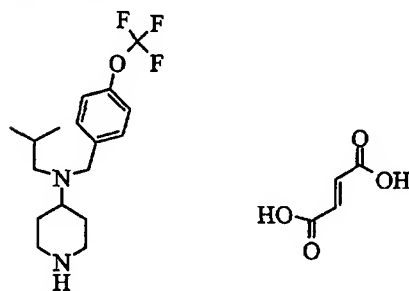
As example 56 with 1,1-dimethylethyl 4-[(2-methylpropyl)amino]piperidine-1-carboxylate and 5-fluoro-2-methoxybenzaldehyde to give N-(2-methylpropyl)-N-[(5-fluoro-2-methoxyphenyl)methyl]piperidin-4-amine fumarate (317 mg, 52%) as a white  
 20

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- solid.  $\delta_H$  (300 MHz, MeOD) 7.24-7.21 (1H, m, ArH), 6.96-6.90 (2H, m, ArH), 6.70 (2H, s, fumarate CH), 3.82 (3H, s, OCH<sub>3</sub>), 3.68 (2H, s, CH<sub>2</sub>Ar) 3.46-3.43 (2H, m, NCH<sub>2</sub>), 2.98-2.77 (3H, m, NCH<sub>2</sub> and NCH), 2.32 (2H, d, J = 7.2 Hz, NCH<sub>2</sub>), 2.05-2.01 (2H, m, CCH<sub>2</sub>), 1.85-1.67 (3H, m, CH(CH<sub>3</sub>)<sub>2</sub> and CCH<sub>2</sub>) and 0.90 (6H, d, J = 6.6 Hz, CH<sub>3</sub>);
- 5 LCMS 12 min, Rt = 2.03 min, (M<sup>+</sup>+1) = 295.2.

**EXAMPLE 82:**

**N-(2-methylpropyl)-N-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-amine fumarate**

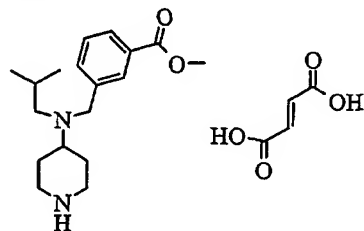


- 10 The title product was prepared from tert-butyl 4-isobutylamino-piperidine-1-carboxylate and 4-(trifluoromethoxy)benzaldehyde using the method described in example 36. LCMS 12 mins gradient Rt = 4.19 (M<sup>+</sup>+1) 331.2. <sup>1</sup>H NMR (d<sub>6</sub>-DMSO)  $\delta$  = 7.44 (2H, d, J = 8.28Hz), 7.30 (2H, d, J = 8.28Hz), 6.45 (2H, s), 3.60 (2H, s), 3.19 (2H, brd), 2.79-2.67 (4H, m), 2.18 (2H, d, J = 6.97Hz), 1.81-1.61 (5H, m), 0.79 (6H, d, J = 6.40Hz).

15

**EXAMPLE 83:**

**N-(2-methylpropyl)-N-{[3-(methoxycarbonyl)phenyl]methyl}piperidin-4-amine fumarate**

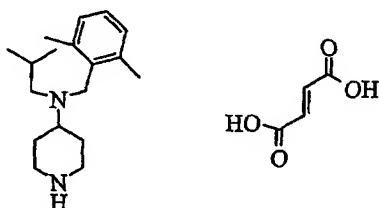


- 20 The title product was prepared from tert-butyl 4-isobutylamino-piperidine-1-carboxylate and methyl 3-formylbenzoate using the method described in example 36. LCMS 12 mins

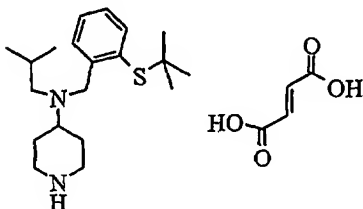
-92-

gradient Rt = 2.94 ( $M^+ + 1$ ) 305.2.  $^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  = 7.95 (1H, s), 7.81 (1H, s), 7.60 (1H, d), 7.48-7.46 (1H, m), 6.42 (2H, s), 3.85 (3H, s, OMe), 3.64 (2H, s), 3.38 (2H, brd), 2.77-2.50 (4H, m), 2.19 (2H, d,  $J$  = 6.97Hz), 1.80-1.59 (5H, m), 0.79 (6H, d,  $J$  = 6.60Hz).

5

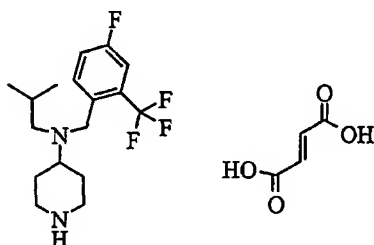
**EXAMPLE 84:****N-(2-methylpropyl)-N-[(2,6-dimethylphenyl)methyl]piperidin-4-amine fumarate**

The title product was prepared from tert-butyl 4-isobutylamino-piperidine-1-carboxylate and 2,6-dimethylbenzaldehyde using the method described in example 36. LCMS 12 mins gradient Rt = 4.04 ( $M^+ + 1$ ) 275.3.  $^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  = 7.04-7.01 (3H, m), 6.41 (2H, s), 3.59 (2H, s), 3.28-3.16 (2H, m), 2.76-2.72 (4H, m), 2.34 (6H, s), 2.10 (2H, d,  $J$  = 6.97 Hz), 1.86-1.65 (5H, m), 0.63 (6H, d,  $J$  = 6.59Hz).

**EXAMPLE 85:****N-(2-methylpropyl)-N-[[2-(tert-butylthio)phenyl]methyl]piperidin-4-amine fumarate**

The title product was prepared from tert-butyl 4-isobutylamino-piperidine-1-carboxylate and 2-(tert-butylthio)benzaldehyde using the method described in example 36. LCMS 12 mins gradient Rt = 4.33 ( $M^+ + 1$ ) 335.2.  $^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  = 7.65 (1H, d,  $J$  = 7.54Hz), 7.48-7.40 (2H, m), 7.26-7.2 (1H, m), 6.42 (2H, s), 3.86 (2H, s), 3.24 (2H, brd), 2.75-2.62 (4H, m), 2.20 (2H, d,  $J$  = 6.97Hz), 1.78-1.54 (5H, m), 1.23 (9H, s, 3x Me), 0.78 (6H, d,  $J$  = 6.60Hz).

20

**EXAMPLE 86:****N-(2-methylpropyl)-N-{{4-fluoro-2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine fumarate**

## 5    Method 1

The title product was prepared from tert-butyl 4-isobutylamino-piperidine-1-carboxylate and 2-(trifluoromethyl)-4-fluorobenzaldehyde using the method described in example 36.

LCMS 12 mins gradient Rt = 6.09 ( $M^+ + 1$ ) 333.5.  $^1H$  NMR ( $d_6$ -DMSO)  $\delta$  = 7.95-7.85 (1H, m), 7.59-7.49 (2H, m), 6.49 (2H, s), 3.63 (2H, s), 3.25 (2H, brd), 2.86-2.62 (3H, m),  
 10    2.20 (2H, d, J = 6.95Hz), 1.85-1.5 (5H, m), 0.80 (6H, d, J = 6.60Hz)

## Method 2

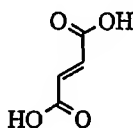
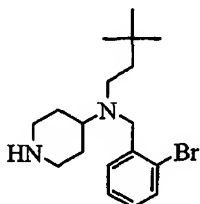
(i) To a solution of 4-isobutylamino-piperidine-1-carboxylic acid tert-butyl ester (10 g, 39mmol, 1.0 eq) in 1,2-dichloroethane (100 ml) was added 2-(trifluoromethyl)-4-fluorobenzaldehyde (22.5g, 117mmol, 3.0 eq). To this was added a solution of sodium triacetoxymethylborohydride (24.8g, 117mmol, 3.0 eq) in dimethylformamide (20 ml). This  
 15    mixture was left to stir under nitrogen, at room temperature, for 16 h. After this time the reaction mixture was quenched with water (50 ml) and subsequently stirred vigorously for several minutes. The reaction mixture was then separated with DCM, washing the organic layer with water (x3). The combined organics were dried over sodium sulfate and  
 20    evaporated *in vacuo* to give an oil. Purification of this crude oil by chromatography on silica was then performed using an Isco system, eluting with 0-50% ethyl acetate:Hexane gradient conditions over 40 mins gave product which was taken directly onto the next step.

(ii) To this oil (39mmol, 1.0 eq.) in dichloromethane (25 ml) was added a solution of 95% trifluoroacetic acid:water (20ml). The solution was stirred at room temperature for 2h.  
 25    Solvent and TFA were removed *in vacuo*. The resulting oil was taken up in DCM and

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washed with saturated sodium carbonate. The organics were collected, dried over sodium sulfate, and evaporated *in vacuo*. The resulting oil was taken up in methanol and loaded onto an SCX-2 pad 120g. The column was washed with methanol (250 ml). Basic material was then eluted using 2M ammonia in methanol (250 ml). Removal of solvent  
 5 from the ammonia/methanol mixture under vacuum, gave the desired compound 5.17g as a free base.

The oil was taken up in diethylether. To this solution was added a solution of fumaric acid (1.8g, 1 eq) in hot ethanol. The mixture was left at room temperature for a few minutes before precipitation occurred. The resulting precipitate was collected by filtration  
 10 to give the title compound as a white solid (3.29g).

**EXAMPLE 87:****N-(3,3-dimethylbutyl)-N-[(2-bromophenyl)methyl]piperidin-4-amine fumarate**

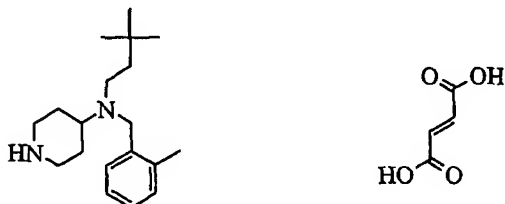
(i) To 10% Pd/C (1.0 g, 10%wt), under nitrogen, was added a solution of the 1-Boc-4-  
 15 piperidone (10.77 g, 54.06 mmole, 1.0 eq.) and 3,3-dimethylbutylamine (5.58 g, 55.14 mmole, 1.02 eq.) in ethanol (65 ml). This was hydrogenated for 1.5 h, at 65 psi hydrogen, using a Parr hydrogenator. The catalyst was removed by filtration through Celite. Solvent was removed under vacuum to give a pale yellow oil (15.7 g). This was purified by automated flash chromatography using an ISCO Combiflash system (SiO<sub>2</sub> (110 g); 0-10%  
 20 methanol in ethyl acetate gradient elution over 40 minutes) to give 1,1-dimethylethyl 4-[(3,3-dimethylbutyl)amino]piperidine-1-carboxylate as a colourless oil (3.53 g, 23%).  $\delta_H$  (300 MHz, CDCl<sub>3</sub>) 4.05-4.01 (2H, m, NCH<sub>2</sub>), 2.83-2.75 (2H, m, NCH<sub>2</sub>), 2.65-2.56 (3H, m, NCH, NCH<sub>2</sub>), 1.86-1.82 (2H, m, CCH<sub>2</sub>), 1.45 (9H, s, OC(CH<sub>3</sub>)<sub>3</sub>), 1.41-1.36 (2H, m, CCH<sub>2</sub>), 1.31-1.18 (2H, m, CCH<sub>2</sub>), 0.91 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>); LCMS 6 min, Rt = 2.7 min,  
 25 (M<sup>+</sup>+1) = 285. A second batch of 1,1-dimethylethyl 4-[(3,3-

dimethylbutyl)amino]piperidine-1-carboxylate, contaminated with a small amount of 1-Boc-4-piperidone, was isolated as a colourless oil (11.85 g).

(ii) To a solution of 1,1-dimethylethyl 4-[(3,3-dimethylbutyl)amino]piperidine-1-carboxylate (0.427 g, 1.50 mmole, 1.0 eq.) in 1,2-dichloroethane (10 ml) was added 2-bromobenzaldehyde (0.53 ml, 4.50 mmole, 3.0 eq.). To this was added a solution of sodium triacetoxyborohydride (0.954 g, 4.50 mmole, 3.0 eq.) in dimethylformamide (2 ml). This mixture was left to stir for 3 days under nitrogen, at room temperature. To the reaction mixture was added water (10 ml) and the mixture stirred vigorously for several minutes. The chlorinated organic layer was run through a hydrophobic frit to remove water, diluted with methanol (10 ml) and loaded onto an SCX-2 (10 g) column. The column was washed with methanol (50 ml) then basic material eluted with 2N ammonia in methanol. The ammonia/methanol solution was concentrated *in vacuo* to give 1,1-dimethylethyl 4-[(2-bromophenylmethyl)(3,3-dimethylbutyl)amino]piperidine-1-carboxylate as a colourless oil (0.681 g, 100%). To a solution of this oil (0.681 g, 1.50 mmole, 1.0 eq.) in dichloromethane (10 ml) was added trifluoroacetic acid (TFA) (1.67 ml, 22.5 mmole, 15 eq). The solution was stirred overnight at room temperature. Solvent and TFA were removed *in vacuo*. The resulting oil was taken up in methanol and loaded onto an SCX-2 (10 g) column. The column was washed with methanol (50 ml). Basic material was then eluted using 2M ammonia in methanol (50 ml). Removal of solvent from the ammonia/methanol mixture under vacuum, gave a colourless oil (0.530 g, 100%). The oil was taken up in methanol. To this solution was added a solution of fumaric acid (0.174 g, 1.50 mmole, 1 eq) in methanol. The mixture was left to stir for a couple of minutes, then ethyl acetate and cyclohexane were added. The resulting precipitate was collected by filtration to give the title compound as a white solid (0.642 g, 91 %).  $\delta_H$  (300 MHz, MeOD) 7.61 (1H, dd, ArH), 7.55 (1H, dd, ArH), 7.37-7.32 (1H, m, ArH), 7.19-7.13 (1H, m, ArH), 6.71 (2H, s, fumarate CH), 3.79 (2H, s, CH<sub>2</sub>Ar), 3.49-3.44 (2H, m, NCH<sub>2</sub>), 3.04-2.88 (3H, m, NCH, NCH<sub>2</sub>), 2.65-2.59 (2H, m, NCH<sub>2</sub>), 2.10-2.05 (2H, m, CCH<sub>2</sub>), 1.90-1.75 (2H, m, CCH<sub>2</sub>), 1.40-1.35 (2H, m, CH<sub>2</sub>*t*Bu), 0.87 (9H, s, CH<sub>3</sub>); LCMS 12 min, Rt = 3.9 min, (M<sup>+</sup>+1) = 353, 355.

**EXAMPLE 88:**

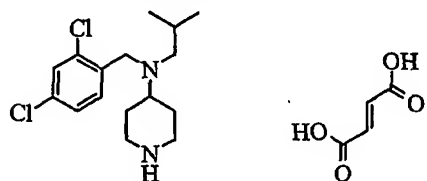
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**N-(3,3-dimethylbutyl)-N-[(2-methylphenyl)methyl]piperidin-4-amine fumarate**

As method previously described for Example 87, using 1,1-dimethylethyl 4-[(3,3-dimethylbutyl)amino]piperidine-1-carboxylate and 2-methylbenzaldehyde. Isolation of the fumarate salt from methanol, ethyl acetate, cyclohexane yielded the title compound as

5 a white solid (0.480 g, 79 %).  $\delta_H$  (300 MHz, MeOD) 7.35 (1H, dd, ArH), 7.16-7.14 (3H, m, ArH), 6.70 (2H, s, fumarate CH), 3.73 (2H, s,  $\text{CH}_2\text{Ar}$ ), 3.49-3.45 (2H, m,  $\text{NCH}_2$ ), 2.99-2.93 (3H, m,  $\text{NCH}_2$ , NCH), 2.62-2.56 (2H, m,  $\text{NCH}_2$ ), 2.39 (3H, s,  $\text{ArCH}_3$ ), 2.09-2.04 (2H, m,  $\text{CCH}_2$ ), 1.92-1.81 (2H, m,  $\text{CCH}_2$ ), 1.37-1.32 (2H, m,  $\text{CH}_2t\text{Bu}$ ), 0.84 (9H, s,  $\text{CH}_3$ ); LCMS 12 min,  $R_t = 3.4$  min,  $(M^+ + 1) = 289$ .

10

**EXAMPLE 89:****N-(2-methylpropyl)-N-[(2,4-dichlorophenyl)methyl]piperidin-4-amine fumarate****Method 1**

The compound was prepared similarly to example 63 using 4-isobutylamino-piperidine-1-carboxylic acid *tert*-butyl ester (0.40g, 1.56mmol) and 2,4-dichlorobenzaldehyde (0.82g, 4.67mmol) to give the title compound as a white solid (0.30g).  $\delta_H$  (300 MHz, MeOD) 7.60 (1H, d), 7.43 (1H, s), 7.31 (1H, m), 6.60 (2H, s, fumarate), 3.78 (2H, s), 3.48 (2H, m), 2.92 (2H, m), 2.81 (1H, m), 2.30 (2H, d), 2.03 (2H, m), 1.75 (3H, m), 0.86 (6H, d). LCMS 12 minute gradient,  $R_t = 5.45$  mins,  $(M^+ + 1) = 316.1$

**Method 2**

(i) To a solution of 4-isobutylamino-piperidine-1-carboxylic acid *tert*-butyl ester (9.0 g, 35.1mmol) in 1,2-dichloroethane (100 ml) was added 2,4-dichlorobenzaldehyde (7.68g,

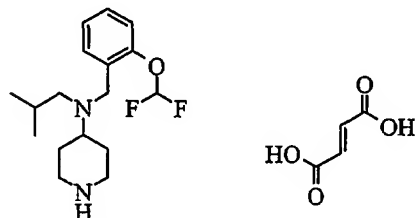


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- 43.9mmol, 1.25 eq). To this was added a solution of sodium triacetoxyborohydride (11.2g, 52.7mmol, 1.5 eq) in 1,2-dichloroethane (100 ml). This mixture was left to stir under nitrogen, at room temperature, for 24 h. After this time the reaction mixture was quenched with water (100 ml). The organic phase was then separated and the aqueous phase extracted with dichloromethane. The combined organics were washed with brine, dried over magnesium sulfate, filtered and evaporated *in vacuo* to give an oil. Purification of this crude oil by chromatography on silica was then performed using an Isco system, eluting with 0-10% ethyl acetate in isohexane gradient conditions over 40 mins to give product that was taken directly onto the next step.
- (ii) To this oil (11.2g, 27.1mmol) in dichloromethane (200 ml) was added trifluoroacetic acid (TFA) (33.8ml). The solution was stirred at room temperature overnight. Solvent and TFA were removed *in vacuo*. The residue was diluted with dichloromethane and made basic by addition of aqueous sodium hydroxide (2M). The organic phase was washed with water (2x) and brine, dried over magnesium sulphate, filtered through celite and evaporated. The oil was taken up in isohexane and ethanol. To this solution was added a solution of fumaric acid (1 eq) in hot ethanol. The mixture was left at room temperature for a few minutes before precipitation occurred. After standing overnight, the resulting precipitate was collected by filtration to give the title compound as a white solid (8.6g).

**EXAMPLE 90:**

**N-(2-methylpropyl)-N-{[2-(difluoromethoxy)phenyl]methyl}piperidin-4-amine fumarate**



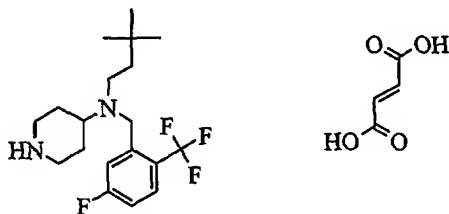
- As example 26 with 1,1-dimethylethyl N-[(2-methylpropyl)amino]piperidine-1-carboxylate and 2-difluoromethoxybenzaldehyde, further purified by mass guided preparative LCMS and loaded onto SCX-2 ion exchange cartridge (5 g). The column was washed with methanol (10 ml) and the product eluted with 2M ammonia in methanol

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solution (10 ml), the solvent was removed *in vacuo* to give a colourless oil. This oil was taken up in dichloromethane (10 ml) and washed with aqueous saturated potassium carbonate (10 ml). The aqueous layer was extracted with dichloromethane (2 x 10 ml) and the combined organic layers dried (MgSO<sub>4</sub>) and the solvent removed *in vacuo* to give a colourless oil (159 mg, 34%). The product was taken up in diethyl ether (10 ml) and a few drops of methanol to solubilize and a hot solution of fumaric acid (59 mg, 0.5 mmol, 1 eq) in methanol (0.5 ml) was added. The solution was heated and a few drops of methanol added until all solid was in solution, then the mixture was allowed to slowly cool to 0°C. The product was collected by filtration and dried in a vacuum oven (40°C for 2h) to give N-(2-methylpropyl)-N-{{2-(difluoromethoxy)phenyl}methyl}piperidin-4-amine fumarate (122 mg, 19%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 7.46-7.43 (1H, m, ArH), 7.21-7.07 (2H, m, ArH), 7.03-7.00 (1H, m, ArH), 6.76 (1H, t, J = 74.5 Hz, OCHF<sub>2</sub>), 6.58 (2H, s, fumarate CH), 3.62 (2H, s, CH<sub>2</sub>Ar) 3.36-3.31 (2H, m, NCH<sub>2</sub>), 2.86-2.64 (3H, m, NCH<sub>2</sub> and NCH), 2.19 (2H, d, J = 7.2 Hz, NCH<sub>2</sub>), 1.93-1.89 (2H, m, CCH<sub>2</sub>), 1.75-1.52 (3H, m, CH(CH<sub>3</sub>)<sub>2</sub> and CCH<sub>2</sub>) and 0.75 (6H, d, J = 6.6 Hz, CH<sub>3</sub>); LCMS 12 min, Rt = 3.20 min, (M<sup>+</sup>+1) = 313.2.

**EXAMPLE 91:**

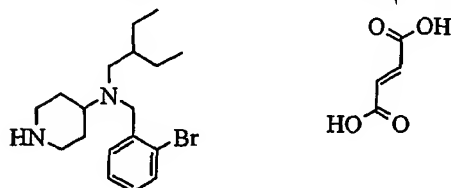
**N-(3,3-dimethylbutyl)-N-{{5-fluoro-2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine fumarate**



As method previously described for Example 87, using 1,1-dimethylethyl 4-[(3,3-dimethylbutyl)amino]piperidine-1-carboxylate and 5-fluoro-2-trifluoromethylbenzaldehyde. Isolation of the fumarate salt from methanol, ethyl acetate, cyclohexane yielded the title compound as a white solid (0.404 g, 57 %).  $\delta_H$  (300 MHz, MeOD) 7.63-7.58 (2H, m, ArH), 7.05-7.01 (1H, m, ArH), 6.58 (2H, s, fumarate CH), 3.76 (2H, s, CH<sub>2</sub>Ar), 3.36-3.32 (2H, m, NCH<sub>2</sub>), 2.93-2.77 (3H, m, NCH<sub>2</sub>, NCH), 2.54-

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2.48 (2H, m, NCH<sub>2</sub>), 2.00-1.93 (2H, m, CCH<sub>2</sub>), 1.73-1.60 (2H, m, CCH<sub>2</sub>), 1.30-1.25 (2H, m, CH<sub>2</sub>tBu), 0.77 (9H, s, CH<sub>3</sub>); LCMS 12 min, Rt = 6.1 min, (M<sup>+</sup>+1) = 361.

**EXAMPLE 92:****5 N-(2-ethylbutyl)-N-[(2-bromophenyl)methyl]piperidin-4-amine fumarate**

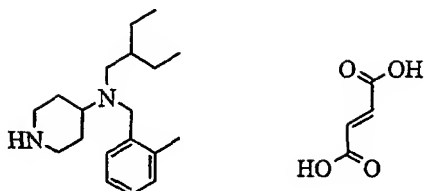
(i) To 10% Pd/C (0.97 g, 10%wt), under nitrogen, was added a solution of the 1-Boc-4-piperidone (9.65 g, 48.44 mmole, 1.0 eq.) and 2-ethyl-*n*-butylamine (5.00 g, 49.41 mmole, 1.02 eq.) in ethanol (65 ml). This was hydrogenated for 1.5 h, at 65 psi hydrogen, using a Parr hydrogenator. The catalyst was removed by filtration through Celite. Solvent  
 10 was removed under vacuum to give a pale yellow oil (13.9 g). This was purified by automated flash chromatography using an ISCO Combiflash system (SiO<sub>2</sub> (110 g); 0-10% methanol in ethyl acetate gradient elution over 40 minutes) to give 1,1-dimethylethyl 4-[(2-ethylbutyl)amino]piperidine-1-carboxylate as a colourless oil (8.82 g, 64%),  $\delta_H$  (300 MHz, CDCl<sub>3</sub>) 4.03-3.99 (2H, m, NCH<sub>2</sub>), 2.85-2.77 (2H, m, NCH<sub>2</sub>), 2.61-2.51 (3H, m, NCH, NCH<sub>2</sub>), 1.85-1.80 (2H, m, CCH<sub>2</sub>), 1.45 (9H, s, OC(CH<sub>3</sub>)<sub>3</sub>), 1.41-1.186 (7H, m, CCH<sub>2</sub>), 0.87 (6H, t, CH<sub>3</sub>); LCMS 6 min, Rt = 2.6 min, (M<sup>+</sup>+1) = 285  
 15

(ii) As method previously described for Example 87 using 1,1-dimethylethyl 4-[(2-ethylbutyl)amino]piperidine-1-carboxylate and 2-bromobenzaldehyde. Isolation of the fumarate salt from methanol, diethyl ether, cyclohexane yielded the title compound as a  
 20 white solid (0.611 g, 87%).  $\delta_H$  (300 MHz, MeOD) 7.47-7.41 (2H, m, ArH), 7.24-7.19 (1H, m, ArH), 7.07-7.01 (1H, m, ArH), 6.58 (2H, s, fumarate CH), 3.66 (2H, s, CH<sub>2</sub>Ar), 3.36-3.32 (2H, m, NCH<sub>2</sub>), 2.88-2.66 (3H, m, NCH, NCH<sub>2</sub>), 2.30 (2H, d, NCH<sub>2</sub>), 1.98-1.93 (2H, m, CCH<sub>2</sub>), 1.78-1.63 (2H, m, CCH<sub>2</sub>), 1.34-1.05 (5H, m, CH(CH<sub>2</sub>Me)<sub>2</sub>), 0.67 (6H, t, CH<sub>3</sub>); LCMS 12 min, Rt = 5.3 min, (M<sup>+</sup>+1) = 353, 355.

25

**EXAMPLE 93:****N-(2-ethylbutyl)-N-[(2-methylphenyl)methyl]piperidin-4-amine fumarate**

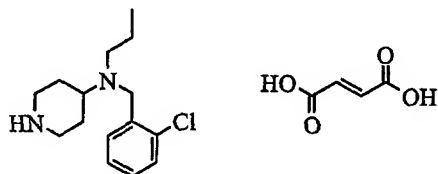
-100-



As method previously described for Example 87, using 1,1-dimethylethyl 4-[(2-ethylbutyl)amino]piperidine-1-carboxylate and 2-methylbenzaldehyde. Isolation of the fumarate salt from methanol, diethyl ether, cyclohexane yielded the title compound as a white solid (0.499 g, 82%).  $\delta_H$  (300 MHz, MeOD) 7.19-7.18 (1H, m, ArH), 7.02-7.01 (3H, m, ArH), 6.58 (2H, s, fumarate CH), 3.56 (2H, s, CH<sub>2</sub>Ar), 3.36-3.21 (2H, m, NCH<sub>2</sub>), 2.85-2.66 (3H, m, NCH<sub>2</sub>, NCH), 2.27-2.24 (5H, m, NCH<sub>2</sub>, ArCH<sub>3</sub>), 1.94-1.90 (2H, m, CCH<sub>2</sub>), 1.78-1.65 (2H, m, CCH<sub>2</sub>), 1.35-1. (5H, m, CH(CH<sub>2</sub>Me)<sub>2</sub>), 0.67 (6H, s, CH<sub>3</sub>); LCMS 12 min, Rt = 4.2 min, (M<sup>+</sup>+1) = 289.

#### 10 **EXAMPLE 94:**

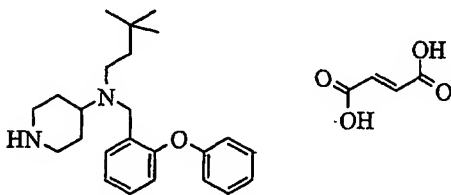
##### **N-propyl-N-[(2-chlorophenyl)methyl]piperidin-4-amine fumarate**



- (i) 4-(propylamino)piperidine-1-carboxylic acid tert-butyl ester was prepared with n-propylamine using the method in example 36(i). LCMS- 6 mins gradient Rt = 1.83 (M<sup>+</sup>+1) 243.3. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 4.10 (2H, brs), 3.75-3.65 (2H, m), 2.81-2.73 (2H, m), 2.61-2.55 (3H, m), 1.91-1.79 (2H, m), 1.46 (9H, s), 1.29-1.21 (4H, m), 0.95-0.92 (2H, m).
- (ii) The title product was prepared with 2-chlorobenzaldehyde using the method described in example 36(ii). LCMS 12 mins gradient Rt = 1.35 (M<sup>+</sup>+1) 262.3. <sup>1</sup>H NMR (d<sub>6</sub>-DMSO)  $\delta$  = 7.64 (1H, m), 7.29 (1H, d, J = 7.54Hz), 7.07 (1H, d, J = 7.72Hz), 6.42 (2H, s), 3.66 (2H, s), 3.25 (2H, brd), 2.78-2.70 (3H, m), 2.41 (3H, s, Me), 2.23 (2H, d, J = 7.16Hz), 1.83-1.57 (5H, m), 0.80 (6H, d, J = 6.6Hz).

#### **EXAMPLE 95:**

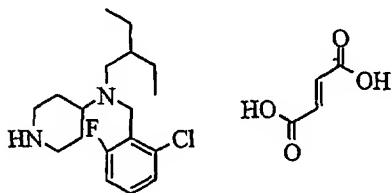
-101-

**N-(3,3-dimethylbutyl)-N-[(2-phenoxyphenyl)methyl]piperidin-4-amine fumarate**

- (i) To a 250 ml round bottomed flask was added 2-fluorobenzaldehyde (12.4 g, 100 mmole, 1.0 eq.), phenol (11.3 g, 120 mmole, 1.2 eq.), potassium carbonate (16.6 g, 120 mmole, 1.2 eq.) and dimethylacetamide (100 ml). The reaction mixture was heated at reflux for 16 hours. The mixture was then diluted with water and extracted with diethyl ether. The combined organic extracts were washed with water (3x) and brine. The washed extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo* to give a yellow oil (15.7 g). This was purified by automated flash chromatography using an ISCO Combiflash system ( $\text{SiO}_2$  (120 g x 2); 0-10% ethyl acetate in cyclohexane gradient elution over 40 minutes) to give 2-phenoxybenzaldehyde as a colourless oil (14.8 g, 75%).  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 10.52 (1H, s, CHO), 7.94 (1H, dd, ArH), 7.54-7.45 (1H, m, ArH), 7.42-7.36 (2H, m, ArH), 7.21-7.15 (2H, m, ArH), 7.09-7.04 (2H, m, ArH), 6.90 (1H, d, ArH); LCMS 6 min,  $R_t = 4.0$  min,  $(M^+ + 1) = 199$ .
- (ii) As method previously described for Example 87, using 1,1-dimethylethyl 4-[(3,3-dimethylbutyl)amino]piperidine-1-carboxylate and 2-phenoxybenzaldehyde. Purification of N-(3,3-dimethylbutyl)-N-[(2-phenoxyphenyl)methyl]piperidin-4-amine using the MS-guided preparative LC purification system followed by SCX-2 treatment (to obtain the free base) yielded a colourless oil (0.29 g). Isolation of the fumarate salt (from ethyl acetate) using method described in Example 87 yielded the title compound as a white solid (0.276 g, 38%).  $\delta_{\text{H}}$  (300 MHz, MeOD) 7.47 (1H, dd, ArH), 7.25-7.14 (3H, m, ArH), 7.09-7.04 (1H, m, ArH), 6.99-6.94 (1H, m, ArH), 6.81-6.78 (3H, m, ArH), 6.58 (2H, s, fumarate CH), 3.63 (2H, s,  $\text{CH}_2\text{Ar}$ ), 3.31-3.27 (2H, m,  $\text{NCH}_2$ ), 2.83-2.74 (3H, m,  $\text{NCH}_2$ , NCH), 2.51-2.46 (2H, m,  $\text{NCH}_2$ ), 1.88-1.84 (2H, m,  $\text{CCH}_2$ ), 1.73-1.61 (2H, m,  $\text{CCH}_2$ ), 1.30-1.25 (2H, m,  $\text{CH}_2\text{tBu}$ ), 0.75 (9H, s,  $\text{CH}_3$ ); LCMS 12 min,  $R_t = 4.2$  min,  $(M^+ + 1) = 367$ .

**EXAMPLE 96:**

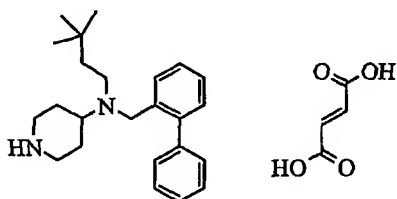
-102-

**N-(2-ethylbutyl)-N-[(2-chloro-6-fluorophenyl)methyl]piperidin-4-amine fumarate**

As method previously described for Example 87, using 1,1-dimethylethyl 4-[(2-ethylbutyl)amino]piperidine-1-carboxylate and 2-chloro-6-fluorobenzaldehyde. Isolation of the fumarate salt from methanol, ethyl acetate, cyclohexane yielded the title compound

5 as a white solid (0.232 g, 38%).  $\delta_H$  (300 MHz, MeOD) 7.23-7.12 (2H, m, ArH), 6.99-6.93 (1H, m, ArH), 6.58 (2H, s, fumarate CH), 3.70 (2H, s,  $CH_2Ar$ ), 3.38-3.34 (2H, m,  $NCH_2$ ), 2.85 (2H, dt,  $NCH_2$ ), 2.77-2.69 (1H, m, NCH), 2.25 (2H, d,  $NCH_2$ ), 1.96-1.92 (2H, m,  $CCH_2$ ), 1.82-1.68 (2H, m,  $CCH_2$ ), 1.24-1.13 (5H, m,  $CH(CH_2Me)_2$ ), 0.63 (6H, t,  $CH_3$ ); LCMS 12 min,  $R_t = 5.3$  min,  $(M^+ + 1) = 327$ .

10

**EXAMPLE 97:****N-(3,3-dimethylbutyl)-N-[(2-biphenyl)methyl]piperidin-4-amine fumarate**

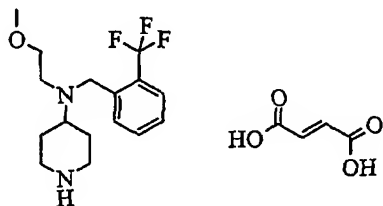
To a 100 ml round bottomed flask, under nitrogen, was added the 1,1-dimethylethyl 4-[(2-bromophenylmethyl)(3,3-dimethylbutyl)amino]piperidine-1-carboxylate (0.675 g, 1.49 mmole, 1.0eq.), phenylboronic acid (0.363 g, 2.98 mmole, 2.0 eq.), dichlorobis(triphenylphosphine)palladium(II) (0.104 g, 0.15 mmole, 0.1 eq.), sodium carbonate (0.158 g, 2.98 mmole, 2.0 eq.) and a 1:1 mixture of tetrahydrofuran : water (50 ml). The mixture was heated at 90°C for two hours. The reaction mixture was allowed to cool then poured into diethyl ether (100 ml). This organic mixture was washed with a

15 solution of sodium hydroxide (2M, aqueous, 80 ml) then concentrated *in vacuo* to give a dark yellow oil (1.18 g). This oil was purified by automated flash chromatography using an ISCO Combiflash system ( $SiO_2$  (120 g); 0-10% methanol (+5% 7M  $NH_3/MeOH$ ) in

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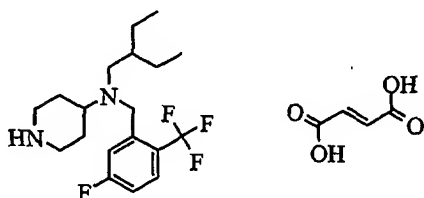
-103-

dichloromethane gradient elution over 40 minutes) to give a yellow oil (0.683 g). This oil was further purified by automated flash chromatography using an ISCO Combiflash system (SiO<sub>2</sub> (120 g); ethyl acetate gradient elution over 40 minutes) to give 1,1-dimethylethyl 4-[(2-biphenyl)methyl](3,3-dimethylbutyl)amino]piperidine-1-carboxylate as a yellow oil (0.549 g, 82%). To a solution of this oil (0.549 g, 1.22 mmole, 1.0 eq.) in dichloromethane (10 ml) was added trifluoroacetic acid (TFA) (1.36 ml, 18.27 mmole, 15 eq). The solution was stirred for one hour at room temperature. Solvent and TFA were removed *in vacuo*. The resulting oil was taken up in methanol and loaded onto an SCX-2 (10 g) column. The column was washed with methanol (50 ml). Basic material was then eluted using 2N ammonia in methanol (50 ml). Removal of solvent from the ammonia/methanol mixture under vacuum, gave a colourless oil (0.27 g). This oil was purified on the Biotage Parallel Flex Purification System (UV-guided HPLC) followed by SCX-2 treatment (to obtain the free base) to give a colourless oil (0.132 g). To a solution of this oil in methanol was added a solution of fumaric acid (0.044 g, 0.38 mmole, 1 eq) in methanol. The mixture was left to stir for a couple of minutes, ethyl acetate and cyclohexane were then added. The resulting precipitate was collected by filtration to give the title compound as a white solid (0.121 g, 17%).  $\delta_H$  (300 MHz, MeOD) 7.50-7.47 (1H, m, ArH), 7.35-7.18 (7H, m, ArH), 7.10-7.07 (1H, m, ArH), 6.61 (3H, s, fumarate CH), 3.58 (2H, s, CH<sub>2</sub>Ar), 3.25-3.24 (2H, m, NCH<sub>2</sub>), 2.74 (2H, dt, NCH<sub>2</sub>), 2.67-2.57 (1H, m, NCH), 2.34-2.29 (2H, m, NCH<sub>2</sub>), 1.65-1.45 (4H, m, CCH<sub>2</sub>), 1.13-1.08 (2H, m, CH<sub>2</sub>/Bu), 0.70 (9H, s, CH<sub>3</sub>); LCMS 12 min, Rt = 4.3 min, (M<sup>+</sup>+1) = 351.

**EXAMPLE 98:****N-(2-methoxyethyl)-N-{[2-(trifluoromethyl)phenyl]methyl}piperidin-4-amine****fumarate**

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The title product was prepared with 4-(2-methoxyethylamino)piperidine-1-carboxylic acid tert-butyl ester and 2-(trifluoromethyl)benzaldehyde using the method described in example 36(ii). LCMS 12 mins gradient  $R_t = 4.24$  ( $M^+ + 1$ ) 287.1.  $^1H$  NMR ( $d_6$ -DMSO)  $\delta = 7.92$  (1H, d,  $J = 7.54$  Hz), 7.68-7.63 (2H, m), 7.43-7.41 (1H, m), 6.44 (2H, s), 3.83 (2H, s), 3.30-3.16 (4H, m), 3.14 (3H, s, OMe), 2.77-2.65 (5H, m), 1.83-1.63 (4H, m).

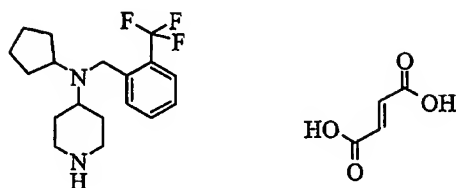
**EXAMPLE 99:****N-(2-ethylbutyl)-N-([5-fluoro-2-(trifluoromethyl)phenyl]methyl)piperidin-4-amine fumarate**

As method previously described for Example 87, using 1,1-dimethylethyl 4-[(2-ethylbutyl)amino]piperidine-1-carboxylate and 5-fluoro-2-trifluoromethylbenzaldehyde. Isolation of the fumarate salt from methanol, ethyl acetate, cyclohexane yielded the title compound as a white solid (0.419 g). Further purified using the Biotage Parallel Flex Purification System (UV-guided HPLC) followed by SCX-2 treatment (to obtain the free base) yielded a colourless oil (0.211g). This was converted to the fumarate salt as previously to give the title compound as a white solid (0.51 g, 21%).  $\delta_H$  (300 MHz, MeOD) 7.64-7.56 (2H, m, ArH), 7.06-7.02 (1H, m, ArH), 6.59 (2H, s, fumarate CH), 3.76 (2H, s,  $CH_2$ Ar), 3.37-3.33 (2H, m,  $NCH_2$ ), 2.86 (2H, dt,  $NCH_2$ ), 2.79-2.69 (1H, m, NCH), 2.33 (2H, d,  $NCH_2$ ), 1.98-1.93 (2H, m,  $CCH_2$ ), 1.75-1.62 (2H, m,  $CCH_2$ ), 1.38-1.11 (5H, m,  $CH(CH_2Me)_2$ ), 0.73 (6H, t,  $CH_3$ ); LCMS 12 min,  $R_t = 6.4$  min, ( $M^+ + 1$ ) = 361.

**EXAMPLE 100:****N-cyclopentyl-N-([2-(trifluoromethyl)phenyl]methyl)piperidin-4-amine fumarate**



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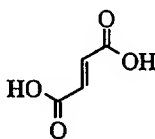
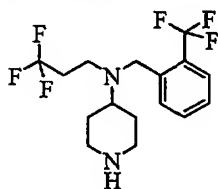
To a solution of 1,1-dimethylethyl 4-([2-(trifluoromethyl)phenyl]methyl)amino)piperidine-1-carboxylate (1.08 g, 3.0 mmol, 1 eq) and acetic acid (0.17 ml, 3.0 mmol, 1 eq) in 1,2-dichloroethane (15 ml) was added a solution of cyclopentanone (0.8 ml, 9.0 mmol, 3 eq). This was stirred for 30 mins before addition of sodium triacetoxyborahydride (1.90 g, 9.0 mmol, 3 eq), the mixture left to stir for 48 h. The reaction was quenched with water (25 ml), the aqueous layer was separated and extracted with dichloromethane (3 x 25 ml), the combined organic layers were dried (MgSO<sub>4</sub>) and the solvent removed *in vacuo* to give a colourless oil. This was purified by automated flash chromatography using an ISCO Combiflash system (35 g SiO<sub>2</sub>) with a gradient of 0-40% ethyl acetate in heptane over 30 minutes to give the 1,1-dimethylethyl 4-([2-(trifluoromethyl)phenyl]methyl)(cyclopentyl)amino]-piperidine-1-carboxylate (1.032 g, 2.4 mmol, 80%) as a colourless oil. To this was added a solution of anisole (2.8 ml) and trifluoroacetic acid (2.8 ml, 36.6 mmol, 15.2 eq), in dichloromethane (14 ml) and the mixture stirred at room temperature for 16 h. The solvent removed *in vacuo* and the residue diluted with methanol (5 ml) and loaded onto SCX-2 ion exchange cartridge (10 g). The column was washed with methanol (50 ml) and eluting the product with 2M ammonia in methanol solution (50 ml) the solvent removed *in vacuo* to give (662 mg, 84%) as a colourless oil. The product was taken up in diethyl ether (30 ml) and a few drops of methanol to solubilize and a hot solution of fumaric acid (235 mg, 2.0 mmol, 1 eq) in methanol (2 ml) was added. The solution was heated and a few drops of methanol added until all solid was in solution, then the mixture was allowed to slowly cool to 0°C. The product was collected by filtration and dried in a vacuum oven (40°C for 2 h) to give N-cyclopentyl-N-([2-(trifluoromethyl)phenyl]methyl)piperidin-4-amine fumarate (570 mg, 54%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 8.06 (1H, d, J = 7.7, ArH), 7.66-7.58 (2H, m, ArH), 7.41-7.36 (1H, m, ArH), 6.71 (2H, s, fumarate CH), 3.94 (2H, s, CH<sub>2</sub>Ar) 3.45-3.39 (3H, m, NCH<sub>2</sub> and cyclopropyl-NCH), 3.04-2.93 (3H, m, NCH<sub>2</sub> and piperidine-

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NCH), 2.07-2.02 (2H, m, CCH<sub>2</sub>), 1.81-1.45 (10H, m, CH<sub>2</sub>); LCMS 12 min, Rt = 5.07 min, (M<sup>+</sup>+1) = 327.1.

**EXAMPLE 101:**

5 **N-(3,3,3-trifluoropropyl)-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine fumarate**



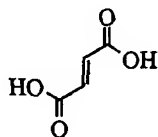
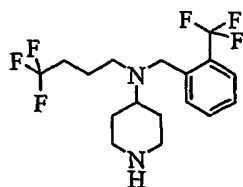
To a solution of 1,1-dimethylethyl 4-({2-(trifluoromethyl)phenyl}methyl)amino)piperidine-1-carboxylate (1.13 g, 3.1 mmol, 1 eq) and acetic acid (0.17 ml, 3.1 mmol, 1 eq) in 1,2-dichloroethane (10 ml) was added a solution of 3,3,3-trifluoropropanal (1.04 g, 9.3 mmol, 3 eq). This was stirred for 30 mins before addition of sodium triacetoxyborohydride (1.97 g, 9.3 mmol, 3 eq), the mixture left to stir for 72 h. The reaction was quenched with water (10 ml), the aqueous layer was separated and extracted with dichloromethane (2 x 10 ml), the combined organic layers were washed with potassium carbonate (50 ml), dried (MgSO<sub>4</sub>) and the solvent removed *in vacuo* to give a colourless oil. This was purified by automated flash chromatography using an ISCO Combiflash system (40 g SiO<sub>2</sub>) with a gradient of 0-40% ethyl acetate in heptane over 30 minutes to give the 1,1-dimethylethyl 4-({2-(trifluoromethyl)phenyl}methyl){3,3,3-trifluoropropyl}amino]-piperidine-1-carboxylate (1.109 g, 2.4 mmol, 78%) as a colourless oil. To this was added a solution of anisole (2.8 ml) and trifluoroacetic acid (2.8 ml, 36.6 mmol, 15.2 eq), in dichloromethane (14 ml) and the mixture stirred at room temperature for 16 h. The solvent removed *in vacuo* and the residue diluted with methanol (5 ml) and loaded onto SCX-2 ion exchange cartridge (10 g). The column was washed with methanol (50 ml) and eluting the product with 2M ammonia in methanol solution (50 ml) the solvent removed *in vacuo* to give (773 mg, 89%) as a colourless oil. The product was taken up in diethyl ether (30 ml) and a few drops of methanol to solubilize and a hot solution of fumaric acid (327 mg, 2.8 mmol, 1 eq) in methanol (2 ml) was added. The solution was heated and a few drops of methanol

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added until all solid was in solution, then the mixture was allowed to slowly cool to 0°C. The product was collected by filtration and dried in a vacuum oven (40°C for 2 h) to give N-(3,3,3-trifluoropropyl)-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine fumarate (885 mg, 78%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 7.92 (1H, d,  $J = 7.7$ , ArH), 7.71-7.61 (2H, m, ArH), 7.48-7.43 (1H, m, ArH), 6.71 (2H, s, fumarate CH), 3.94 (2H, s,  $CH_2Ar$ ), 3.50-3.46 (2H, m,  $NCH_2$ ), 3.35-2.84 (5H, m,  $NCH_2$ , NCH and  $NCH_2$ ), 2.41-2.29 (2H, m,  $CH_2CF_3$ ), 2.10-2.06 (2H, m,  $CCH_2$ ) and 1.87-1.75 (2H, m,  $CCH_2$ ); LCMS 12 min,  $R_t = 5.38$  min,  $(M^+ + 1) = 355.1$ .

#### 10 EXAMPLE 102:

N-(4,4,4-trifluorobutyl)-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine fumarate



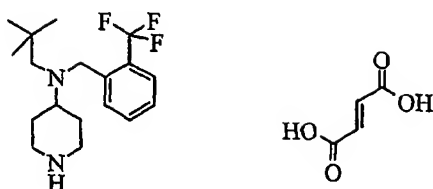
As example 101 with 1,1-dimethylethyl 4-({2-(trifluoromethyl)phenyl}methyl)amino)piperidine-1-carboxylate and 4,4,4-trifluorobutylaldehyde to give N-(4,4,4-trifluorobutyl)-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine fumarate (728 mg, 75%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 7.77 (1H, d,  $J = 7.9$ , ArH), 7.58-7.49 (2H, m, ArH), 7.34-7.29 (1H, m, ArH), 6.59 (2H, s, fumarate CH), 3.78 (2H, s,  $CH_2Ar$ ), 3.36-3.33 (2H, m,  $NCH_2$ ), 2.89-2.72 (3H, m,  $NCH_2$  and NCH), 2.54 (2H, t,  $J = 6.8$  Hz,  $NCH_2$ ), 2.08-1.92 (4H, m,  $CH_2$ ) and 1.74-1.51 (4H, m,  $CH_2$ ); LCMS 12 min,  $R_t = 5.53$  min,  $(M^+ + 1) = 369.1$ .

#### EXAMPLE 103:

N-(2,2-dimethylpropyl)-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine fumarate

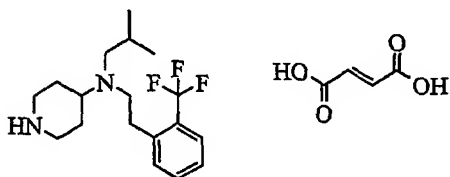
25 fumarate

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As example 101 with 1,1-dimethylethyl 4-({[2-(trifluoromethyl)phenyl]methyl}amino)piperidine-1-carboxylate and trimethylacetaldehyde to give N-(2,2-dimethylpropyl)-N-({[2-(trifluoromethyl)phenyl]methyl}piperidin-4-amine fumarate (493 mg, 56%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 8.00 (1H, d,  $J = 7.7$  Hz, ArH), 7.56-7.51 (2H, m, ArH), 7.33-7.18 (1H, m, ArH), 6.59 (2H, s, fumarate CH), 3.90 (2H, s,  $\text{CH}_2\text{Ar}$ ), 3.35-3.30 (2H, m,  $\text{NCH}_2$ ), 2.81-2.93 (2H, m,  $\text{NCH}_2$ ), 2.59-2.51 (1H, m, NCH), 2.32 (2H, s,  $\text{NCH}_2$ ), 2.00-1.94 (2H, m,  $\text{CCH}_2$ ), 1.71-1.60 (2H, m,  $\text{CCH}_2$ ) and 0.80 (9H, d,  $\text{CH}_3$ ); LCMS 12 min,  $R_t = 5.91$  min,  $(M^+ + 1) = 329.2$ .

10

**EXAMPLE 104:****N-(2-methylpropyl)-N-([2-(trifluoromethyl)phenyl]ethyl)piperidin-4-amine fumarate**

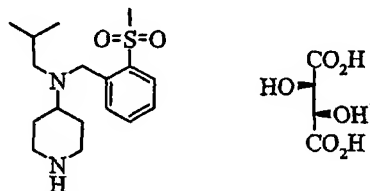
(i) 2-(Trifluoromethyl)phenethyl alcohol (3.00g, 15.77mmol) in dry dichloromethane (100ml) was added pyridinium chlorochromate (4.08g, 18.93mmol) in one portion at room temperature, under an atmosphere of nitrogen. The orange mixture turns black after 20 mins. The reaction was monitored by thin layer chromatography (100% diethyl ether; reactant r.f. 0.5, product r.f. 0.9). After 1 hr the solvent was evaporated *in vacuo* to give a black oil and this was taken up in diethyl ether (100ml) and filtered through a pad of silica and eluted with diethyl ether (100ml). The filtrate was taken and concentrated *in vacuo* to a yellow oil (1.91g, 10.09mmol). The (2-trifluoromethylphenyl)acetaldehyde was taken to the next step without any purification.  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ) 9.75 (1H, s), 7.87-7.23 (4H, m), 3.94 (2H, s).

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- (ii) The compound was prepared similarly to example 63 using 4-isobutylamino-piperidine-1-carboxylic acid *tert*-butyl ester (0.50g, 1.95mmol) and (2-trifluoromethyl-phenyl)-acetaldehyde (1.09g, 5.85mmol) to give the title compound as an off-white solid (0.53g, 1.19mmol).  $\delta_H$  (300 MHz, MeOD) 7.61-7.36 (4H, m), 6.69 (2H, s, fumarate), 3.48 (2H, m), 3.00 (5H, m), 2.72 (2H, m), 2.32 (2H, d), 1.98 (2H, m), 1.73 (3H, m), 0.92 (6H, d). LCMS 12 minute gradient,  $R_t = 3.44$  mins,  $(M^+ + 1) = 329.2$

**EXAMPLE 105:**

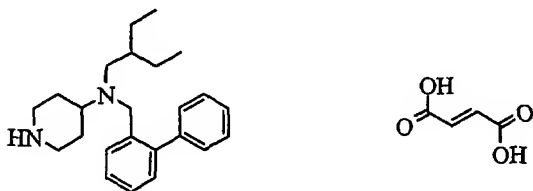
**N-(2-methylpropyl)-N-[[2-(methylsulphonyl)phenyl]methyl]piperidin-4-amine D-tartrate**



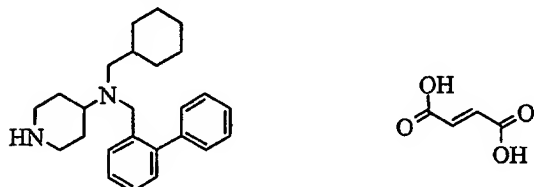
- (i) 2-fluorobenzaldehyde (12.4 g, 0.1 mol, 1 eq) and methanesulphonic acid (11.2 g, 0.11 mol, 1.1 eq) were dissolved in DMSO (75 ml) and heated to 100°C for 16 h. The reaction mixture was cooled to room temperature and poured onto crushed ice (100 g). The product was collected by filtration and dried in a vacuum oven at 45°C for 16 h to give 2-(methylsulphonyl)benzaldehyde (9.2 g, 50%) as a yellow solid.  $\delta_H$  (300 MHz,  $CDCl_3$ ) 10.77 (1H, s, CHO), 8.18-8.16 (1H, m, ArH), 8.10-8.08 (1H, m, ArH), 7.83-7.80 (2H, m, ArH) and 3.28 (3H, s,  $SO_2CH_3$ ); LCMS 6 min,  $R_t = 1.93$  min,  $(M^+ + 1) = 185.1$ .
- (ii) To a solution of 1,1-dimethylethyl 4-[(2-methylpropyl)amino]piperidine-1-carboxylate (0.38 g, 1.5 mmol, 1 eq) in 1,2-dichloroethane (10ml) was added 2-(methylsulphonyl)benzaldehyde (829 mg, 4.5 mmol, 3 eq), after 15 minutes sodium triacetoxyborahydride (0.95 g, 4.5 mmol, 3 eq) was added and the mixture left to stir for 16 h. The reaction was quenched with water (10 ml), the aqueous layer was separated and extracted with dichloromethane (2 x 20 ml). The combined organic layers were washed with brine (20 ml), dried ( $MgSO_4$ ) and the solvent removed *in vacuo*. This was purified by automated flash chromatography using an ISCO Combiflash system (40 g  $SiO_2$ ) with a gradient of 0-40% ethyl acetate in heptane over 30 minutes to give 1,1-dimethylethyl 4-[[[2-(methylsulphonyl)phenyl]methyl](2-methylpropyl)amino]-

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piperidine-1-carboxylate (0.41 g, 1.0 mmol, 65%) as a colourless oil. To this was added a solution of anisole (1.4 ml) and trifluoroacetic acid (1.4 ml, 18.3 mmol, 18.3 eq), in dichloromethane (7 ml) and the mixture stirred at room temperature for 16 h. The solvent removed *in vacuo* and the residue diluted with methanol (5 ml) and loaded onto SCX-2 ion exchange cartridge (5 g). The column was washed with methanol (15 ml) and eluting the product with 2M ammonia in methanol solution (15 ml) the solvent removed *in vacuo* to give (199 mg, 0.6 mmol, 60%) as a colourless oil. The product was taken up in cyclohexane/isopropanol (30 ml) and a hot solution of D-tartaric acid (92 mg, 0.6 mmol, 1 eq) in isopropanol (2 ml) was added. The solvent was removed *in vacuo* and the gum triturated with diethyl ether (3 x 20 ml) to give the title compound (278 mg, 60%) as a yellow solid.  $\delta_H$  (300 MHz, MeOD) 7.93-7.83 (2H, m, ArH), 7.61-7.58 (1H, m, ArH), 7.42-7.37 (1H, m, ArH), 4.31 (2H, s, tartrate CH), 4.06 (2H, s, CH<sub>2</sub>Ar), 3.36-3.32 (2H, m, NCH<sub>2</sub>), 3.13 (3H, s, SO<sub>2</sub>CH<sub>3</sub>), 2.84-2.67 (3H, m, NCH and NCH<sub>2</sub>), 2.27 (2H, d, J = 7.0 Hz, NCH<sub>2</sub>), 1.97-1.92 (2H, m, CCH<sub>2</sub>), 1.76-1.56 (3H, m, CCH<sub>2</sub> and CH(CH<sub>3</sub>)<sub>2</sub>) and 0.80 (6H, d, J = 6.6 Hz, CH<sub>3</sub>); LCMS 12 min, Rt = 3.03 min, (M<sup>+</sup>+1) = 325.1.

**EXAMPLE 106:****N-(2-ethylbutyl)-N-[(2-biphenyl)methyl]piperidin-4-amine fumarate**

As method previously described for Example 97, using 1,1-dimethylethyl 4-[(2-bromophenyl)methyl](2-ethylbutyl)amino]piperidine-1-carboxylate. Isolation of the fumarate salt from methanol, diethyl ether, cyclohexane yielded the title compound as a white solid (0.238 g, 34%).  $\delta_H$  (300 MHz, MeOD) 7.59-7.57 (1H, m, ArH), 7.45-7.27 (7H, m, ArH), 7.19-7.16 (1H, m, ArH), 6.69 (1.5H, s, fumarate CH), 3.62 (2H, s, CH<sub>2</sub>Ar), 3.34-3.32 (2H, m, NCH<sub>2</sub>), 2.79 (2H, dt, NCH<sub>2</sub>), 2.66-2.57 (1H, m, NCH), 2.21 (2H, d, NCH<sub>2</sub>), 1.64-1.50 (4H, m, CCH<sub>2</sub>), 1.38-1.17 (5H, m, CH(CH<sub>2</sub>Me)<sub>2</sub>), 0.78 (6H, t, CH<sub>3</sub>); LCMS 12 min, Rt = 5.1 min, (M<sup>+</sup>+1) = 351.

**EXAMPLE 107:****N-(cyclohexylmethyl)-N-[(2-biphenyl)methyl]piperidin-4-amine fumarate**

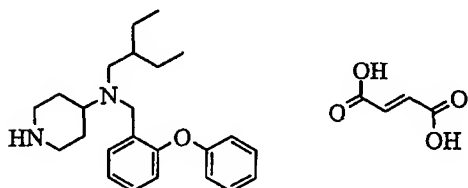
- (i) To a solution of cyclohexylmethylamine (0.461 g, 4.08 mmole, 1.02 eq.) in 1,2-dichloroethane (10 ml) was added 1-Boc-4-piperidone (0.797 g ml, 4.00 mmole, 1.0 eq.). To this was added a solution of sodium triacetoxyborohydride (0.865 g, 4.08 mmole, 1.02 eq.) in dimethylformamide (2 ml). This mixture was left to stir under nitrogen, at room temperature, over the weekend. To the reaction mixture was then added water (10 ml) and the mixture stirred vigorously for several minutes. The chlorinated organic layer was then run through a hydrophobic frit then diluted with methanol (10 ml) and loaded onto an SCX-2 (10 g) column. The column was washed with methanol (50 ml) then basic material eluted with 2N ammonia in methanol. The ammonia/methanol solution was concentrated *in vacuo* to give a pale yellow oil (1.2 g). This was purified by automated flash chromatography using an ISCO Combiflash system (SiO<sub>2</sub> (40 g); 0-10% methanol in ethyl acetate gradient elution over 40 minutes) to give 1,1-dimethylethyl 4-[(cyclohexylmethyl)amino]piperidine-1-carboxylate as a colourless oil (0.98 g, 83%).  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 4.03-4.00 (2H, m, NCH<sub>2</sub>), 2.83-2.75 (2H, m, NCH<sub>2</sub>), 2.60-2.49 (1H, m, NCH), 2.45 (2H, d, NCH<sub>2</sub>), 1.18-0.83 (15H, m, CCH<sub>2</sub>), 1.45 (9H, s, OC(CH<sub>3</sub>)<sub>3</sub>); LCMS 6 min, Rt = 2.7 min, (M<sup>+</sup>+1) = 297.
- (ii) To a solution of 1,1-dimethylethyl 4-[(cyclohexylmethyl)amino]piperidine-1-carboxylate (0.245 g, 0.840 mmole, 1.0 eq.), 2-phenylbenzyl bromide (0.185 ml, 1.01 mmole, 1.2 eq.) in dry acetonitrile (5 ml) was added anhydrous potassium carbonate (0.19 g, 1.35 mmole, 1.6 eq.). The mixture was stirred overnight at room temperature. The reaction mixture was concentrated under vacuum to give a white solid. The white solid was taken up in dichloromethane (10 ml) and this washed with water (10 ml). The dichloromethane layer was passed through a hydrophobic frit then diluted with methanol (10 ml). This solution was loaded onto an SCX-2 (10 g) column. The column was washed

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with methanol (50 ml) then basic material was eluted using 2N ammonia in methanol (50 ml). Concentration of the ammonia/methanol solution under vacuum yielded a colourless oil (0.344 g, 90%). To a solution of this oil (0.344 g, 0.74 mmole, 1.0 eq.) in dichloromethane (10 ml) was added trifluoroacetic acid (TFA) (0.83 ml, 11.2 mmole, 15 eq). The solution was stirred overnight at room temperature. Solvent and TFA were removed *in vacuo*. The resulting oil was taken up in methanol and loaded onto an SCX-2 (10 g) column. The column was washed with methanol (50 ml). Basic material was then eluted using 2N ammonia in methanol (50 ml). Removal of solvent from the ammonia/methanol mixture under vacuum, gave a colourless oil (0.298 g, 99%). The oil was taken up in methanol. To this solution was added a solution of fumaric acid (0.095 g, 0.08 mmole, 1 eq) in methanol followed by diethyl ether and cyclohexane. The resulting precipitate was collected by filtration to give the title compound as a white solid (0.302 g, 76 %).  $\delta_H$  (300 MHz, MeOD) 7.58 (1H, d, ArH), 7.45-7.29 (7H, m, ArH), 7.18 (1H, d, ArH), 6.70 (2H, s, fumarate CH), 3.64 (2H, s,  $CH_2Ar$ ), 3.33-3.32 (2H, m,  $NCH_2$ ), 2.79 (2H, dt,  $NCH_2$ ), 2.65-2.54 (1H, m, NCH), 2.17 (2H, d,  $NCH_2$ ), 1.74-1.47 (9H, m,  $CCH_2$ ), 1.28-1.11 (4H, m, CH,  $CCH_2$ ), 0.78-0.67 (2H, m,  $CH_2$ ); LCMS 12 min,  $R_t = 5.0$  min,  $(M^+ + 1) = 363$ .

**EXAMPLE 108:**

**N-(2-ethylbutyl)-N-[(2-phenoxyphenyl)methyl]piperidin-4-amine fumarate**



As method previously described for Example 87, using 2-phenoxybenzaldehyde and 1,1-dimethylethyl 4-[(2-bromophenylmethyl)(2-ethylbutyl)amino]piperidine-1-carboxylate. Isolation of the fumarate salt from methanol, diethyl ether, cyclohexane yielded the title compound as a white solid (0.562 g, 78%).  $\delta_H$  (300 MHz, MeOD) 7.56 (1H, dd, ArH), 7.36-7.24 (3H, m, ArH), 7.19-7.15 (1H, m, ArH), 7.09-7.04 (1H, m, ArH), 6.92-6.89 (3H, m, ArH), 6.70 (2H, s, fumarate CH), 3.68 (2H, s,  $CH_2Ar$ ), 3.41-3.37 (2H, m,  $NCH_2$ ),

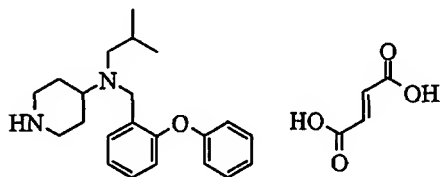


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2.89-2.77 (3H, m, NCH, NCH<sub>2</sub>), 2.35 (2H, d, NCH<sub>2</sub>), 1.93-1.89 (2H, m, CCH<sub>2</sub>), 1.81-1.67 (2H, m, CCH<sub>2</sub>), 1.47-1.24 (5H, m, CH(CH<sub>2</sub>Me)<sub>2</sub>), 0.80 (6H, t, CH<sub>3</sub>); LCMS 12 min, Rt = 4.8 min, (M<sup>+</sup>+1) = 367.

5 **EXAMPLE 109:**

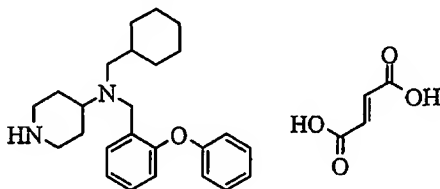
**N-(2-methylpropyl)-N-[(2-phenoxyphenyl)methyl]piperidin-4-amine fumarate**



As method previously described for Example 87, using 2-phenoxybenzaldehyde and 1,1-dimethylethyl 4-[(2-methylpropyl)amino]piperidine-1-carboxylate. Isolation of the fumarate salt from methanol, diethyl ether, cyclohexane yielded the title compound as a white solid (0.521 g, 79%).  $\delta_H$  (300 MHz, MeOD) 7.58 (1H, dd, ArH), 7.36-7.24 (3H, m, ArH), 7.20-7.14 (1H, m, ArH), 7.09-7.04 (1H, m, ArH), 6.91-6.88 (3H, m, ArH), 6.70 (2H, s, fumarate CH), 3.68 (2H, s, CH<sub>2</sub>Ar), 3.40-3.31 (2H, m, NCH<sub>2</sub>), 2.89-2.75 (3H, m, NCH, NCH<sub>2</sub>), 2.27 (2H, d, NCH<sub>2</sub>), 1.93-1.89 (2H, m, CCH<sub>2</sub>), 1.78-1.63 (3H, m, CCH<sub>2</sub>, CHMe<sub>2</sub>), 1.47-1.24 (5H, m, CH(CH<sub>2</sub>Me)<sub>2</sub>), 0.86 (6H, d, CH<sub>3</sub>); LCMS 12 min, Rt = 4.0 min, (M<sup>+</sup>+1) = 339.

**EXAMPLE 110:**

**N-(cyclohexylmethyl)-N-[(2-phenoxyphenyl)methyl]piperidin-4-amine fumarate**

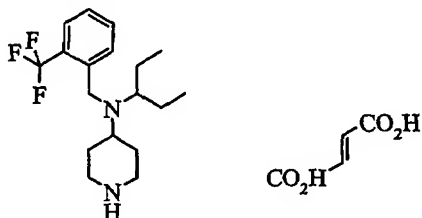


As method previously described for Example 87, using 2-phenoxybenzaldehyde prepared as for Example 95 and 1,1-dimethylethyl 4-[(cyclohexylmethyl)amino]piperidine-1-carboxylate as prepared for Example 107. Isolation of the fumarate salt from methanol, ethyl acetate, cyclohexane yielded the title compound as a white solid (0.155g, 37%).  $\delta_H$  (300 MHz, MeOD) 7.59 (1H, dd, ArH), 7.42-7.27 (3H, m, ArH), 7.23-7.18 (1H, m, ArH),

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7.12-7.07 (1H, m, ArH), 6.95-6.92 (2H, m, ArH), 6.72 (3H, s, fumarate CH), 3.71 (2H, s, CH<sub>2</sub>Ar), 3.43-3.37 (2H, m, NCH<sub>2</sub>), 2.92-2.77 (3H, m, NCH, NCH<sub>2</sub>), 2.33 (2H, d, NCH<sub>2</sub>), 1.95-1.68 (9H, m, CCH<sub>2</sub>), 1.50-1.38 (1H, m, CH), 1.28-1.18 (3H, m, CCH<sub>2</sub>), 0.86-0.78 (2H, m, CH<sub>2</sub>); LCMS 12 min, Rt = 4.7 min, (M<sup>+</sup>+1) = 379.

5

**EXAMPLE 111:****N-(1-ethylpropyl)-N-{[2-(trifluoromethyl)phenyl]methyl}piperidin-4-amine fumarate**

(i) To a solution of 1-Boc-4-piperidone (4.98 g, 25 mmol, 1 eq) in 1,2-dichloroethane (45 ml) was added 1-ethylpropylamine (2.91 ml, 25 mmol, 1 eq) and the solution stirred for 15 minutes. Sodium triacetoxyborahydride (5.29 g, 25 mmol, 1 eq) was added and the reaction mixture stirred for a further 16 hours. The mixture was diluted with water (25 ml) and saturated potassium carbonate (25ml), then extracted with dichloromethane (3 x 50 ml). The combined organic extracts were washed with brine (100 ml), dried (MgSO<sub>4</sub>) and the solvent removed *in vacuo* to give a yellow oil which was purified by automated flash chromatography using an ISCO Combiflash system (120 g SiO<sub>2</sub>) with a gradient of 0-30% methanol in ethyl acetate over 30 minutes to give the 1,1-dimethylethyl 4-[(1-ethylpropyl)amino]piperidine-1-carboxylate (2.84 g, 42%) as a colourless oil.  $\delta_H$  (300 MHz, CDCl<sub>3</sub>) 4.03-3.92 (2H, m, NCH<sub>2</sub>), 2.84-2.77 (2H, m, NCH<sub>2</sub>), 2.69-2.60 (1H, m, NCH) 2.51-2.43 (1H, m, NCH), 1.84-1.79 (2H, m, CCH<sub>2</sub>), 1.52-1.14 (15H, m, CH<sub>2</sub> and C(CH<sub>3</sub>)<sub>3</sub>) and 0.87 (6H, t, J = 7.4 Hz, CH<sub>3</sub>); LCMS 12 min, Rt = 2.45 min, (M<sup>+</sup>+1) = 271.3.

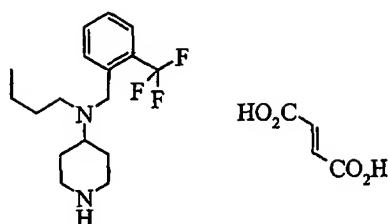
(ii) To a solution of 1,1-dimethylethyl 4-[(1-ethylpropyl)amino]piperidine-1-carboxylate (300 mg, 1.1 mmol, 1 eq) and 2-(trifluoromethyl)benzyl bromide (0.2 ml, 1.3 mmol, 1.2 eq) in acetonitrile (5 ml) was added potassium carbonate (243 mg, 1.7 mmol, 1.6 eq). The mixture was refluxed for 4 days then cooled to room temperature, diluted with water

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(10 ml) and extracted with dichloromethane (3 x 10 ml). The combined organic extracts were dried (MgSO<sub>4</sub>) and the solvent removed *in vacuo* to give an oil which was diluted with methanol (5 ml) and loaded onto SCX-2 ion exchange cartridge (5 g). The column was washed with methanol (15 ml) and eluting the product with 2M ammonia in methanol solution (15 ml) the solvent removed *in vacuo* to give 1,1-dimethylethyl 4-[[1-(trifluoromethyl)phenyl]methyl}(2-ethylpropyl)amino]-piperidine-1-carboxylate (275 mg, 0.6 mmol, 58%) as a colourless oil. To this was added a solution of anisole (1 ml) and trifluoroacetic acid (1 ml, 13.1 mmol, 21.2 eq), in dichloromethane (5 ml) and the mixture stirred at room temperature for 16 h. The solvent removed *in vacuo* and the residue diluted with methanol (5 ml) and loaded onto SCX-2 ion exchange cartridge (5 g). The column was washed with methanol (15 ml) and eluting the product with 2M ammonia in methanol solution (15 ml) the solvent removed *in vacuo*. This was further purified by MS guided preparative LC then loaded onto SCX-2 ion exchange cartridge (5 g). The column was washed with methanol (15 ml) and eluting the product with 2M ammonia in methanol solution (15 ml) the solvent removed *in vacuo* to give (134 mg, 68%) as a colourless oil. The product was taken up in diethyl ether (10 ml) and a few drops of methanol to solubilize and a hot solution of fumaric acid (47 mg, 2.0 mmol, 1 eq) in methanol (1 ml) was added. The solution was heated and a few drops of methanol added until all solid was in solution, then the mixture was allowed to slowly cool to 0°C. The product was collected by filtration and dried in a vacuum oven (40°C for 2 h) to give N-(1-ethylpropyl)-N-[[2-(trifluoromethyl)phenyl]methyl]piperidin-4-amine fumarate (90 mg, 34%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 7.95 (1H, d, J = 7.9 Hz, ArH), 7.66-7.58 (2H, m, ArH), 7.42-7.37 (1H, m, ArH), 6.70 (2H, s, fumarate CH), 3.96 (2H, s, CH<sub>2</sub>Ar), 3.45-3.41 (2H, m, NCH<sub>2</sub>), 3.00-2.86 (3H, m, NCH and NCH<sub>2</sub>), 2.35-2.30 (1H, m, NCH), 2.07-2.02 (2H, m, CCH<sub>2</sub>), 1.87-1.76 (2H, m, CCH<sub>2</sub>), 1.60-1.39 (4H, m, CH<sub>2</sub>) and 0.96 (6H, t, J = 7.46 Hz, CH<sub>3</sub>); LCMS 12 min, Rt = 3.52 min, (M<sup>+</sup>+1) = 329.2.

**EXAMPLE 112:****N-butyl-N-[[2-(trifluoromethyl)phenyl]methyl]piperidin-4-amine fumarate**

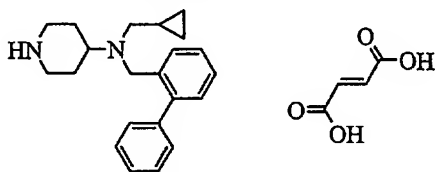
-116-



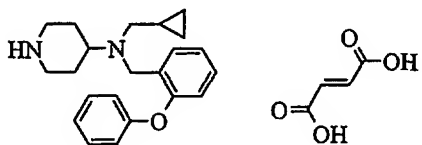
- (i) A mixture of 1-tert-butoxycarbonyl-4-piperidone (25g, 126mmol), n-butylamine (11g, 151mmol) and 10% palladium on carbon (2.5g) in ethanol (250ml) was hydrogenated on a Parr apparatus for 1.5h at 65psi. The reaction mixture was filtered through a pad of celite and the filtrate evaporated to give 4-butylamino-piperidine-1-carboxylic acid tert-butyl ester as a colourless liquid (32g). LCMS 6min Rt 2.48min m/e 257 ( $M^+ + H$ ).
- (ii) Sodium triacetoxyborohydride (11.4g, 54mmol) was added to a stirred solution of 4-butylamino-piperidine-1-carboxylic acid tert-butyl ester (9.2g, 36mmol) and 2-trifluoromethylbenzaldehyde (8.0g 46mmol) in 1,2-dichloroethane (100ml) at room temperature under nitrogen atmosphere. After 16h, water (100ml) was added and the mixture stirred vigorously. The organic layer was separated and the aqueous solution was extracted with dichloromethane (50ml). The combined organic solutions were washed with water, dried, filtered and evaporated to a semi-solid (20.5g). Suspended in ethyl acetate (5ml) iso-hexane (50ml) and the solid filtered, washed iso-hexane. The filtrate was evaporated give the crude product as a colourless liquid (15.2g). Purified by flash chromatography eluting with 5-10% ethyl acetate in iso-hexane gave the product as an oil (10.0g, 68%). LCMS 6min, Rt 4.0min, m/e 415 ( $M^+ + H$ ).
- (iii) Trifluoroacetic acid (18.3ml, 237mmol) was added to stirred solution of the above oil (9.8g, 23.7mmol) in dichloromethane (40ml) at room temperature. After 1h, diluted with dichloromethane (100ml) and basified with aqueous sodium hydroxide (2M, 120ml). The dichloromethane layer was separated, washed with water (100ml), dried, filtered and evaporated to a colourless oil of N-butyl-N-{[2-(trifluoromethyl)phenyl]methyl}piperidin-4-amine (8.0g). The free base in ethanol (40ml) iso-hexane (40ml) was converted to the fumarate salt by addition of a hot solution of fumaric acid (2.55g) in ethanol (40ml). Crystallised on standing as white flakes of the title product (8.60, 84%). LCMS 12min, Rt 4.3 min, m/e 315 ( $M^+ + H$ ).  $\delta_H$  (300MHz, d6-DMSO) 7.74 (1H, d), 7.46-7.55 (2H, m), 7.28 (1H, t), 6.28 (2H, s), 3.60 (2H, s), 3.10

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(2H, d), 2.61 (3H, t), 2.26-2.33 (2H, m), 1.43-1.71 (4H, m), 1.00-1.21 (4H, m), 0.64 (3H, t).

**EXAMPLE 113:****5 N-(cyclopropylmethyl)-N-[(2-biphenyl)methyl]piperidin-4-amine fumarate**

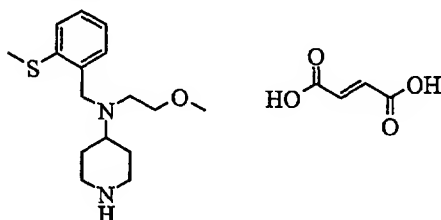
As method previously described for Example 107, using 1,1-dimethylethyl 4-[(cyclopropylmethyl)amino]piperidine-1-carboxylate and 2-phenylbenzyl bromide. Isolation of the fumarate salt from methanol and diethyl ether yielded the title compound as a white solid (0.485 g, 74%).  $\delta_H$  (300 MHz, MeOD) 7.68 (1H, dd, ArH), 7.47-7.29 (7H, m, ArH), 7.21 (1H, d, ArH), 6.72 (2H, s, fumarate CH), 3.76 (2H, s, CH<sub>2</sub>Ar), 3.38-3.34 (2H, m, NCH<sub>2</sub>), 2.92-2.82 (3H, m, NCH, NCH<sub>2</sub>), 2.32 (2H, d, NCH<sub>2</sub>), 1.79-1.57 (4H, m, CCH<sub>2</sub>), 0.77-0.66 (1H, m, CH), 0.46-0.40 (2H, m, CH<sub>2</sub>), 0.03-0.02 (2H, m, CH<sub>2</sub>); LCMS 12 min, Rt = 3.5 min, (M<sup>+</sup>+1) = 321.

**15 EXAMPLE 114:****N-(cyclopropylmethyl)-N-[(2-phenoxyphenyl)methyl]piperidin-4-amine fumarate**

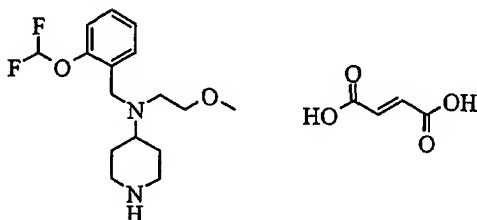
As method previously described for Example 87 using 1,1-dimethylethyl 4-[(cyclopropylmethyl)amino]piperidine-1-carboxylate and 2-phenoxybenzaldehyde. Isolation of the fumarate salt from methanol and diethyl ether yielded the title compound as a white solid (0.586 g, 86%).  $\delta_H$  (300 MHz, MeOD) 7.54 (1H, dd, ArH), 7.28-7.16 (3H, m, ArH), 7.12-7.07 (1H, m, ArH), 7.02-6.96 (1H, m, ArH), 6.85-6.80 (3H, m, ArH), 6.60 (2H, s, fumarate CH), 3.75 (2H, s, CH<sub>2</sub>Ar), 3.34-3.30 (2H, m, NCH<sub>2</sub>), 3.04-2.96 (1H, m, NCH), 2.86-2.77 (2H, m, NCH<sub>2</sub>), 2.41 (2H, d, NCH<sub>2</sub>), 1.92-1.86 (2H, m, CCH<sub>2</sub>), 1.77-

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1.63 (2H, m, CCH<sub>2</sub>), 0.84-0.74 (1H, m, CH), 0.43-0.37 (2H, m, CH<sub>2</sub>), 0.03-0.02 (2H, m, CH<sub>2</sub>); LCMS 12 min, Rt = 3.6 min, (M<sup>+</sup>+1) = 337.

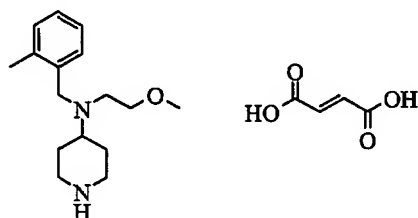
**EXAMPLE 115:****5 N-(2-methoxyethyl)-N-[(2-methylthio)methyl]piperidin-4-amine fumarate**

- (i) 4-(2-methoxyethylamino)piperidine-1-carboxylic acid tert-butyl ester was prepared with 2-methoxyethylamine by the method in example 36(i). LCMS- 6 mins gradient Rt = 2.14 (M<sup>+</sup>+1) 259.3. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ= 4.10 (2H, brs), 3.56-3.50 (2H, m), 3.45 (3H, s, OMe), 2.90-2.69 (3H, m), 2.68-2.61 (1H, m), 1.85-1.80 (4H, m), 1.46 (9H, s), 1.38-1.22 (2H, m).
- (ii) The title product was prepared with 4-(2-methoxyethylamino)piperidine-1-carboxylic acid tert-butyl ester and 2-(methylthio)benzaldehyde using the method described in example 36(ii). LCMS 12 mins gradient Rt = 2.63 (M<sup>+</sup>+1) 295.1. <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ= 7.45 (1H, d), 7.26-7.25 (2H, m), 7.18-7.10 (1H, m), 6.42 (2H, s), 3.63 (2H, s), 3.31-3.15 (4H, m), 3.15 (3H, s, Ar-SMe), 2.81-2.68 (3H, m), 2.65-2.60 (2H, m), 2.40 (3H, s, CH<sub>2</sub>-OMe), 1.90-1.75 (2H, m), 1.74-1.60 (2H, m).

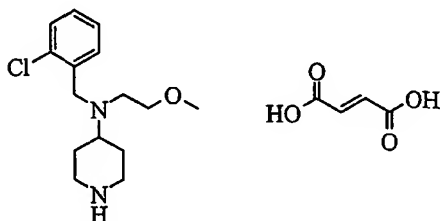
**EXAMPLE 116:****20 N-(2-methoxyethyl)-N-[[2-(difluoromethoxy)phenyl]methyl]piperidin-4-amine fumarate**

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The title product was prepared with 4-(2-methoxyethylamino)piperidine-1-carboxylic acid tert-butyl ester and 2-(difluoromethoxy)benzaldehyde using the method described in example 36(ii). LCMS 12 mins gradient Rt = 2.50 ( $M^+ + 1$ ) 315.1.  $^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  = 7.54 (1H, d,  $J$  = 7.34Hz), 7.42-7.31 (2H, m), 7.29-7.13 (1H, m), 6.42 (2H, s), 3.68 (2H, s), 3.27-3.23 (4H, m), 3.13 (3H, s, OMe), 2.90-2.65 (3H, m), 2.63-2.61 (2H, m), 1.82-1.72 (2H, m), 1.68-1.65 (2H, m).

**EXAMPLE 117:****N-(2-methoxyethyl)-N-[(2-methyl)methyl]piperidin-4-amine fumarate**

The title product was prepared with 4-(2-methoxyethylamino)piperidine-1-carboxylic acid tert-butyl ester and 2-methylbenzaldehyde using the method described in example 36(ii). LCMS 12 mins gradient Rt = 2.49 ( $M^+ + 1$ ) 263.1.  $^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  = 7.33-7.32 (1H, m), 7.15-7.12 (3H, m), 6.43 (2H, s), 3.63 (2H, s), 3.26-3.17 (4H, m), 3.13 (3H, s, Ar-Me), 2.76-2.71 (3H, m), 2.69-2.58 (2H, m), 2.29 (3H, s, OMe), 1.83-1.79 (2H, m), 1.71-1.68 (2H, m).

**EXAMPLE 118:****N-(2-methoxyethyl)-N-[(2-chlorophenyl)methyl]piperidin-4-amine fumarate**

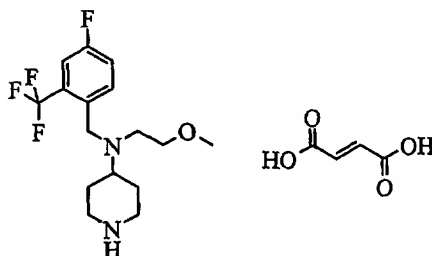
The title product was prepared with 4-(2-methoxyethylamino)piperidine-1-carboxylic acid tert-butyl ester and 2-chlorobenzaldehyde using the method described in example 36(ii). LCMS 12 mins gradient Rt = 2.75 ( $M^+ + 1$ ) 283.1.  $^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  = 7.60

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(1H, d, J= 6.03Hz), 7.40-7.23 (3H, m), 6.42 (2H, s), 3.74 (2H, s), 3.38-3.22 (4H, m), 3.15 (3H, s, OMe), 2.78-2.65 (5H, m), 1.84-1.80 (2H, m), 1.72-1.65 (2H, m).

**EXAMPLE 119:**

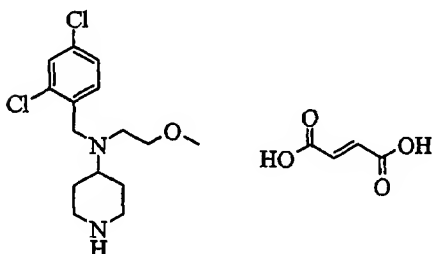
5 **N-(2-methoxyethyl)-N-([4-fluoro-2-(trifluoromethyl)phenyl]methyl)piperidin-4-amine fumarate**



The title product was prepared with 4-(2-methoxyethylamino)piperidine-1-carboxylic acid tert-butyl ester and 4-fluoro-2-(trifluoromethyl)benzaldehyde using the method described in example 36(ii). LCMS 12 mins gradient Rt = 4.65 ( $M^+$ +1) 335.1. <sup>1</sup>H NMR (d6-DMSO)  $\delta$ = 7.97-7.92 (1H, m), 7.56-7.50 (2H, m), 6.42 (2H, s), 3.80 (2H, s), 3.39-3.22 (4H, m), 3.14 (3H, s, OMe), 2.74-2.64 (5H, m), 1.82-1.60 (4H, m).

**EXAMPLE 120:**

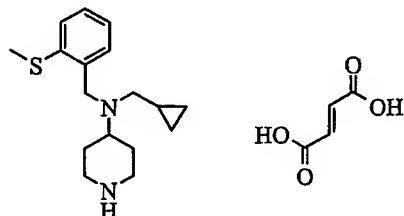
15 **N-(2-methoxyethyl)-N-[(2,4-dichlorophenyl)methyl]piperidin-4-amine fumarate**



The title product was prepared with 4-(2-methoxyethylamino)piperidine-1-carboxylic acid tert-butyl ester and 2,4-dichlorobenzaldehyde using the method described in example 36(ii). LCMS 12 mins gradient Rt = 4.05 ( $M^+$ +1) 317.1. <sup>1</sup>H NMR (d6-DMSO)  $\delta$ = 7.62 (1H, d, J= 8.29Hz), 7.54 (1H, d, J= 2.07Hz), 7.41 (1H, dd, J= 2.07Hz, J= 2.07Hz) 6.42 (2H, s), 3.72 (2H, s), 3.38-3.22 (4H, m), 3.15 (3H, s, OMe), 2.91-2.65 (5H, m), 1.83-1.64 (4H, m).

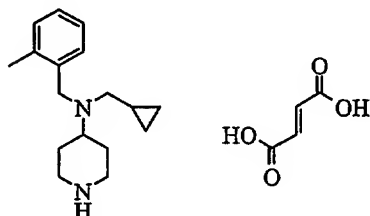


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**EXAMPLE 121:****N-(cyclopropylmethyl)-N-[(2-methylthiophenyl)methyl]piperidin-4-amine fumarate**

(i) 4-(cyclopropylmethylamino)piperidine-1-carboxylic acid tert-butyl ester was prepared with cyclopropylmethylamine by the method in example 36(i). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ= 4.10 (2H, brs), 2.81-2.61 (3H, m), 2.51 (2H, d), 1.80-1.71 (4H, m), 1.49 (9H, s), 1.38-1.21 (2H, m), 1.01-0.95 (1H, m), 0.55-0.45 (2H, m), 0.15-0.10 (2H, m).

(ii) The title product was prepared with 2(methylthio)benzaldehyde using the method described in example 36(ii). LCMS 12 mins gradient Rt = 2.67 (M<sup>+</sup>+1) 291.1. <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ= 7.47 (1H, d, J= 7.35Hz), 7.24-7.23 (2H, m), 7.15-7.10 (1H, m), 6.42 (2H, s), 3.66 (2H, s), 3.25 (2H, brd), 2.90-2.86 (1H, m), 2.79-2.71 (2H, m), 2.43 (3H, s, SMe), 1.86-1.82 (2H, m), 1.74-1.67 (4H, m), 0.78-0.76 (1H, m), 0.36 (2H, d, J= 5.47Hz), 0.1 (4H, m).

**EXAMPLE 122:****N-(cyclopropylmethyl)-N-[(2-methylphenyl)methyl]piperidin-4-amine fumarate**

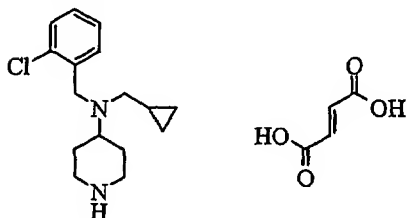
The title product was prepared with 4-(cyclopropylmethylamino)piperidine-1-carboxylic acid tert-butyl ester and 2-methylbenzaldehyde using the method described in example 36(ii). LCMS 12 mins gradient Rt = 2.41 (M<sup>+</sup>+1) 259.2. <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ= 7.37 (1H, m), 7.14-7.10 (3H, m), 6.42 (2H, s), 3.65 (2H, s), 3.25 (2H, brd), 2.90-2.55 (3H, m),

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2.32 (3H, s), 2.31 (2H, s), 1.86-1.67 (4H, m), 0.78-0.76 (1H, m), 0.39-0.36 (2H, m), 0.1 (4H, m)

**EXAMPLE 123:**

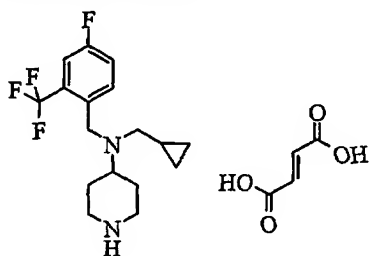
5 **N-(cyclopropylmethyl)-N-[(2-chlorophenyl)methyl]piperidin-4-amine fumarate**



The title product was prepared with 4-(cyclopropylmethylamino)piperidine-1-carboxylic acid tert-butyl ester and 2-chlorobenzaldehyde using the method described in example 36(ii). LCMS 12 mins gradient Rt = 2.45 ( $M^+ + 1$ ) 279.1.  $^1H$  NMR ( $d_6$ -DMSO)  $\delta$  = 7.65 (1H, d), 7.40-7.18 (3H, m), 6.42 (2H, s), 3.71 (2H, s), 3.25 (2H, brd), 2.95-2.88 (1H, m),  
 10 2.79-2.71 (2H, m), 2.39 (2H, d), 1.86-1.75 (2H, m), 1.72-1.58 (2H, m), 0.78-0.76 (1H, m), 0.39-0.36 (2H, m), 0.10 (4H, m).

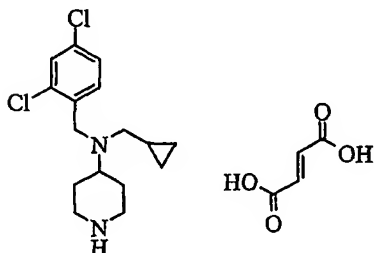
**EXAMPLE 124:**

15 **N-(cyclopropylmethyl)-N-[[4-fluoro-2-(trifluoromethyl)phenyl]methyl]piperidin-4-amine fumarate**

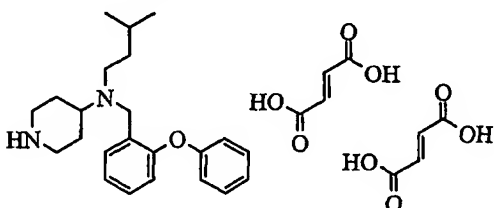


The title product was prepared with 4-(cyclopropylmethylamino)piperidine-1-carboxylic acid tert-butyl ester and 2-fluoro-4-(trifluoromethyl)benzaldehyde using the method described in example 36(ii). LCMS 12 mins gradient Rt = 4.57 ( $M^+ + 1$ ) 331.1.  $^1H$  NMR ( $d_6$ -DMSO)  $\delta$  = 7.37 (1H, m), 7.14-7.10 (2H, m), 6.42 (2H, s), 3.65 (2H, s), 3.25 (2H, brd), 2.90-2.55 (3H, m), 2.32 (3H, s), 2.31 (2H, d), 1.86-1.67 (4H, m), 0.78-0.76 (1H, m),  
 20 0.39-0.36 (2H, m), 0.1 (3H, m).

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**EXAMPLE 125:****N-(cyclopropylmethyl)-N-[(2,4-dichlorophenyl)methyl]piperidin-4-amine fumarate**

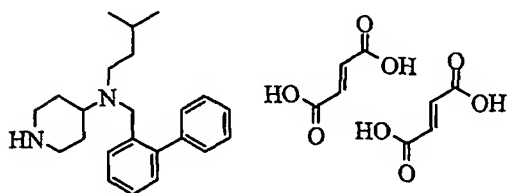
The title product was prepared with 4-(cyclopropylmethylamino)piperidine-1-carboxylic acid tert-butyl ester and 2,4-dichlorobenzaldehyde using the method described in example 36(ii). LCMS 12 mins gradient Rt = 3.61 ( $M^+ + 1$ ) 313.0.  $^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  = 7.37 (1H, m), 7.14-7.10 (1H, m), 7.41 (1H, m), 6.42 (2H, s), 3.65 (2H, s), 3.24 (2H, brd), 2.90-2.55 (3H, m), 2.30 (2H, d), 1.89-1.61 (4H, m), 0.78-0.76 (1H, m), 0.39-0.36 (2H, m), 0.1 (4H, m).

**EXAMPLE 126:****N-(3-methylbutyl)-N-[(2-phenoxyphenyl)methyl]piperidin-4-amine difumarate**

(i) To 10% Pd/C (1.0 g, 10%wt), under nitrogen, was added a solution of the 1-Boc-4-piperidone (10.0 g, 50.1 mmole, 1.0 eq.) and isoamylamine (4.46 g, 51.2 mmole, 1.02 eq.) in ethanol (60 ml). This was hydrogenated overnight, at 60 psi using a Parr hydrogenator. The catalyst was removed by filtration through Celite. Solvent was removed under vacuum to give 1,1-dimethylethyl 4-[(3-methylbutyl)amino]piperidine-1-carboxylate as a colourless, slightly cloudy, oil (13.59 g, 100%).  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 4.05-4.02 (2H, m,  $\text{NCH}_2$ ), 2.82-2.75 (2H, m,  $\text{NCH}_2$ ), 2.66-2.54 (3H, m,  $\text{NCH}$ ,  $\text{NCH}_2$ ), 1.86-1.82 (2H, m,  $\text{CCH}_2$ ), 1.62 (1H, septet,  $\text{CHMe}_2$ ), 1.45 (9H, s,  $\text{OC}(\text{CH}_3)_3$ ), 1.41-1.17 (4H, m,  $\text{CCH}_2$ ), 0.90 (6H, d,  $\text{C}(\text{CH}_3)_2$ ); LCMS 6 min, Rt = 2.7 min, ( $M^+ + 1$ ) = 271.

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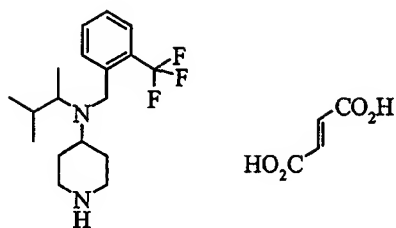
(ii) As method previously described for Example 87, using 2-phenoxybenzaldehyde and 1,1-dimethylethyl 4-[(3-methylbutyl)amino]piperidine-1-carboxylate. Isolation of the fumarate salt from methanol and diethyl ether yielded the title compound as a white solid (0.264 g, 30%).  $\delta_H$  (300 MHz, MeOD) 7.46 (1H, dd, ArH), 7.26-7.16 (3H, m, ArH), 7.10-7.04 (1H, m, ArH), 7.00-6.95 (1H, m, ArH), 6.86-6.79 (3H, m, ArH), 6.61 (4H, s, fumarate CH), 3.68 (2H, s,  $CH_2Ar$ ), 3.33-3.28 (2H, m,  $NCH_2$ ), 3.04-2.96 (3H, m,  $NCH$ ,  $NCH_2$ ), 2.56-2.51 (2H, m,  $NCH_2$ ), 1.91-1.87 (2H, m,  $CCH_2$ ), 1.76-1.62 (2H, m,  $CCH_2$ ), 1.52-1.41 (1H, m, CH), 1.30-1.23 (2H, m,  $CH_2$ ), 0.74 (6H, d,  $CH_3$ ); LCMS 12 min,  $R_t$  = 4.2 min,  $(M^+ + 1) = 353$ .

**EXAMPLE 127:****N-(3-methylbutyl)-N-[(2-biphenyl)methyl]piperidin-4-amine difumarate**

As method previously described for Example 107, using 1,1-dimethylethyl 4-[(3-methylbutyl)amino]piperidine-1-carboxylate and 2-phenylbenzyl bromide. Isolation of the fumarate salt from methanol and diethyl ether yielded the title compound as a white solid (0.239 g, 24%).  $\delta_H$  (300 MHz, MeOD) 7.49 (1H, dd, ArH), 7.35-7.18 (7H, m, ArH), 7.10 (1H, dd, ArH), 6.61 (4H, s, fumarate CH), 3.62 (2H, s,  $CH_2Ar$ ), 3.25 (2H, m,  $NCH_2$ ), 2.78-2.59 (3H, m,  $NCH$ ,  $NCH_2$ ), 2.36-2.31 (2H, m,  $NCH_2$ ), 1.64-1.45 (4H, m,  $CCH_2$ ), 1.42-1.31 (1H, m, CH), 1.13-1.05 (2H, m,  $CH_2$ ), 0.69 (6H, d,  $CH_3$ ); LCMS 12 min,  $R_t$  = 4.1 min,  $(M^+ + 1) = 337$ .

**EXAMPLE 128:****N-(1,2-dimethylpropyl)-N-[[2-(trifluoromethyl)phenyl]methyl]piperidin-4-amine fumarate isomer 1**

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(i) As example 111(i) with 1,2-dimethylpropylamine to give 1,1-dimethylethyl 4-[(1,2-dimethylpropyl)amino]piperidine-1-carboxylate (3.15 g, 46%) as a colourless oil.  $\delta_H$  (300 MHz,  $CDCl_3$ ) 3.92-3.76 (2H, m,  $NCH_2$ ), 2.71-2.46 (4H, m,  $NCH_2$ ,  $NCH$  and  $NCH$ ), 1.80-1.73 (2H, m,  $CCH_2$ ), 1.62-1.51 (1H, m,  $CH$ ), 1.38 (9H, m,  $C(CH_3)_3$ ), 1.18-1.04 (2H, m,  $CH_2$ ) 0.87 (3H, d,  $J = 6.4$  Hz,  $CH_3$ ), 0.81 (3H, d,  $J = 6.8$  Hz,  $CH_3$ ) and 0.77 (3H, d,  $J = 6.8$  Hz,  $CH_3$ ); LCMS 12 min,  $R_t = 2.48$  min,  $(M^+ + 1) = 271.3$ .

(ii) To a solution of 1,1-dimethylethyl 4-[(1,2-dimethylpropyl)amino]piperidine-1-carboxylate (1.6 g, 6.0 mmol, 1 eq) and 2-(trifluoromethyl)benzyl bromide (1.1 ml, 7.2 mmol, 1.2 eq) in acetonitrile (30 ml) was added potassium carbonate (1.33 g, 9.6 mmol, 1.6 eq). The mixture was refluxed for 4 days then cooled to room temperature, diluted with water (50 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were washed with brine (100 ml), dried ( $MgSO_4$ ) and the solvent removed *in vacuo* to give an oil which was purified by automated flash chromatography using an ISCO Combiflash system (120 g  $SiO_2$ ) with a gradient of 0-40% methanol in ethyl acetate over 80 minutes to give 1,1-dimethylethyl 4-[[2-(trifluoromethyl)phenyl]methyl]{(1,2-dimethylpropyl)amino]-piperidine-1-carboxylate (1.77 g, 4.1 mmol, 70%) as a colourless oil. To This was added a solution of anisole (4 ml) and trifluoroacetic acid (5 ml, 52.3 mmol, 12.5 eq), in dichloromethane (20 ml) and the mixture stirred at room temperature for 16 h. The solvent removed *in vacuo* and the residue diluted with methanol (10 ml) and loaded onto SCX-2 ion exchange cartridge (2 x 10 g). Each column was washed with methanol (50 ml) and eluting the product with 2M ammonia in methanol solution (50 ml) the solvent removed *in vacuo* to give a colourless oil (723 mg, 53%). The racemic mixture was separated into their two enantiomers by chiral chromatography on a Chiralcel OD(3641) using 70% Heptane/ 30% ethanol and 0.2% diethylamine as the mobile phase at a rate of 0.5 ml/min. To a solution of the free base of the first eluting enantiomer (164 mg, 0.5 mmol, 1 eq) in diethyl ether (10 ml) and a few drops of

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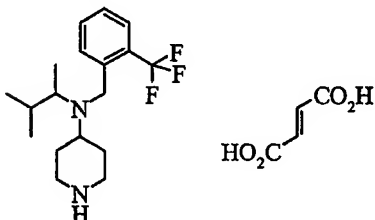
methanol to solubilize was added a hot solution of fumaric acid (58 mg, 0.5 mmol, 1 eq) in methanol (1 ml) was added. The solution was heated and a few drops of methanol added until all solid was in solution, then the mixture was allowed to slowly cool to 0°C. The product was collected by filtration and dried in a vacuum oven (40°C for 2 h) to give

5 N-(1,2-dimethylpropyl)-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine fumarate isomer 1 (150 mg, 31%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 7.84 (1H, d, J = 7.7 Hz, ArH), 7.55-7.47 (2H, m, ArH), 7.31-7.26 (1H, m, ArH), 6.58 (2H, s, fumarate CH), 3.90 (1H, d, J = 16.0 Hz, CHHAr), 3.74 (1H, d, J = 16.0 Hz, CHHAr), 3.34-3.27 (2H, m, NCH<sub>2</sub>), 2.90-2.75 (3H, m, NCH and NCH<sub>2</sub>), 2.35-2.30 (1H, m, NCH), 2.07-2.03 (1H, m, CH), 1.81-1.53 (4H, m, CCH<sub>2</sub> and CCH<sub>2</sub>), 1.02 (3H, d, J = 6.6 Hz, CH<sub>3</sub>), 0.90 (3H, d, J = 6.6 Hz, CH<sub>3</sub>) and 0.77 (3H, d, J = 6.6 Hz, CH<sub>3</sub>); LCMS 12 min, Rt = 6.00 min, (M<sup>+</sup>+1) = 329.2.

10

**EXAMPLE 129:**

15 **N-(1,2-dimethylpropyl)-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine fumarate isomer 2**



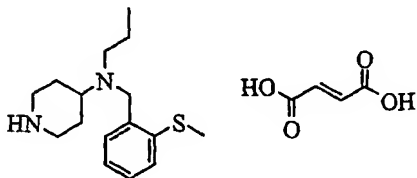
As example 128(ii) with the second eluting enantiomer to give N-(1,2-dimethylpropyl)-N-{{2-(trifluoromethyl)phenyl}methyl}piperidin-4-amine fumarate isomer 2 (139 mg, 28%) as a white solid.  $\delta_H$  (300 MHz, MeOD) 7.96 (1H, d, J = 7.7 Hz, ArH), 7.67-7.59 (2H, m, ArH), 7.42-7.40 (1H, m, ArH), 6.70 (2H, s, fumarate CH), 4.02 (1H, d, J = 16.0 Hz, CHHAr), 3.86 (1H, d, J = 16.0 Hz, CHHAr), 3.52-3.42 (2H, m, NCH<sub>2</sub>), 3.01-2.88 (3H, m, NCH and NCH<sub>2</sub>), 2.46-2.41 (1H, m, NCH), 2.19-2.15 (1H, m, CH), 1.94-1.70 (4H, m, CCH<sub>2</sub> and CCH<sub>2</sub>), 1.13 (3H, d, J = 6.6 Hz, CH<sub>3</sub>), 1.01 (3H, d, J = 6.6 Hz, CH<sub>3</sub>) and 0.89 (3H, d, J = 6.6 Hz, CH<sub>3</sub>); LCMS 12 min, Rt = 5.96 min, (M<sup>+</sup>+1) = 329.2.

20

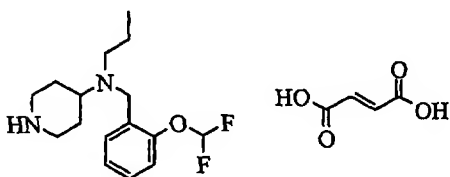
25

**EXAMPLE 130:**

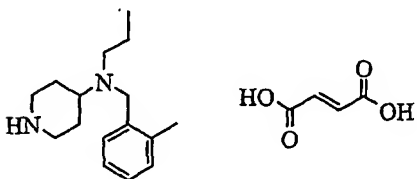
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**N-propyl-N-[(2-methylthiophenyl)methyl]piperidin-4-amine fumarate**

The title product was prepared with 4-(propylamino)piperidine-1-carboxylic acid tert-butyl ester and 2-(methylthio)benzaldehyde using the method described in example 36(ii). LCMS 12 mins gradient Rt = 2.61 ( $M^+ + 1$ ) 279.1.  $^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  = 7.43(1H, d,  $J$  = 7.34Hz), 7.23 (2H, m), 7.13 (1H, m), 6.42 (2H, s), 3.61(2H, s), 3.40 (2H, m), 3.25 (2H, brd), 2.78-2.70 (3H, m), 2.49 (3H, s, SMe), 2.43-2.37 (2H, m), 1.84-1.71 (2H, m), 1.67-1.63 (2H, m), 1.35-1.28 (2H, m), 0.79-0.73 (3H, m).

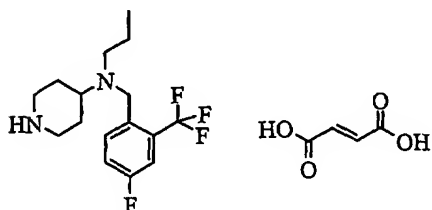
**EXAMPLE 131:****10 N-propyl-N-[[2-(difluoromethoxy)phenyl]methyl]piperidin-4-amine fumarate**

The title product was prepared with 4-(propylamino)piperidine-1-carboxylic acid tert-butyl ester and 2-(difluoromethoxy)benzaldehyde using the method described in example 36(ii). LCMS 12 mins gradient Rt = 2.33 ( $M^+ + 1$ ) 299.1.  $^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  = 7.55-7.52 (1H, m), 7.42-7.30 (2H, m), 7.27-7.20 (1H, m), 6.43 (2H, s), 3.62(2H, s), 3.25 (2H, brd), 2.78-2.71 (3H, m), 2.42-2.40 (2H, m), 1.82-1.64 (4H, m), 1.46-1.30 (2H, m), 0.83-0.74 (3H, m).

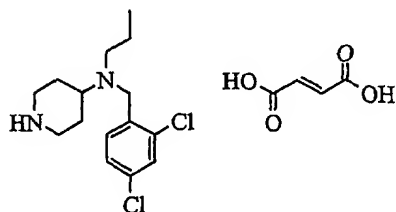
**EXAMPLE 132:****N-propyl-N-[(2-methylphenyl)methyl]piperidin-4-amine fumarate**

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The title product was prepared with 4-(propylamino)piperidine-1-carboxylic acid tert-butyl ester and 2-methylbenzaldehyde using the method described in example 36(ii). LCMS 12 mins gradient Rt = 2.40 ( $M^+ + 1$ ) 247.2.  $^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  = 7.33-7.31 (1H, m), 7.14-7.11 (3H, m), 6.42 (2H, s), 3.57 (2H, s), 3.25 (2H, brd), 2.76-2.69 (3H, m), 2.49-2.40 (2H, m), 2.38 (3H, s, Me), 1.82-1.70 (4H, m), 1.34-1.27 (2H, m), 0.77-0.72 (3H, m).

**EXAMPLE 133:****N-propyl-N-([4-fluoro-2-(trifluoromethyl)phenyl]methyl)piperidin-4-amine****10 fumarate**

The title product was prepared with 4-(propylamino)piperidine-1-carboxylic acid tert-butyl ester and 4-fluoro-2-(trifluoromethyl)benzaldehyde using the method described in example 36(ii). LCMS 12 mins gradient Rt = 4.69 ( $M^+ + 1$ ) 319.1.  $^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  = 7.97-7.85 (1H, m), 7.59-7.49 (2H, m), 6.42 (2H, s), 3.66 (2H, s), 3.25 (2H, brd), 2.78-2.67 (3H, m), 2.48-2.39 (2H, m), 1.84-1.61 (4H, m), 1.38-1.24 (2H, m), 0.79-0.72 (3H, m).

**EXAMPLE 134:****N-propyl-N-[(2,4-dichlorophenyl)methyl]piperidin-4-amine fumarate**

20 The title product was prepared with 4-(propylamino)piperidine-1-carboxylic acid tert-butyl ester and 2,4-dichlorobenzaldehyde using the method described in example 36(ii). LCMS 12 mins gradient Rt = 3.59 ( $M^+ + 1$ ) 301.1.  $^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  = 7.60-7.54

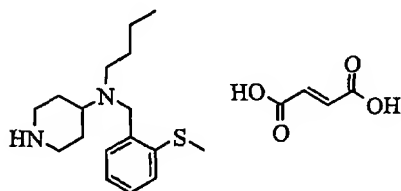


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(2H, m), 7.43-7.40 (1H, m), 6.42 (2H, s), 3.65(2H, s), 3.25 (2H, brd), 2.79-2.71 (3H, m), 2.45-2.40 (2H, m), 1.82-1.78 (2H, m), 1.64-1.60 (2H, m), 1.37-1.32 (2H, m), 0.80-0.76 (3H, m).

5 **EXAMPLE 135:**

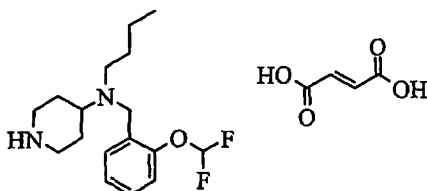
**N-butyl-N-[(2-methylthiophenyl)methyl]piperidin-4-amine fumarate**



The title product was prepared with 4-(butylamino)piperidine-1-carboxylic acid tert-butyl ester and 2-(methylthio)benzaldehyde using the method described in example 36(ii). LCMS 12 mins gradient Rt = 3.04 ( $M^+ + 1$ ) 293.1. <sup>1</sup>H NMR (d6-DMSO)  $\delta$  = 7.42 (1H, d, J = 7.35Hz), 7.23 (2H, d, J = 3.96Hz) 7.12 (1H, m), 6.42 (2H, s), 3.63 (2H, s), 3.25 (2H, brd), 2.78-2.70 (3H, m), 2.43 (3H, s, SMe) 2.40 (2H, m), 1.84-1.65 (4H, m), 1.30-1.21 (4H, m), 0.80-0.75 (3H, m).

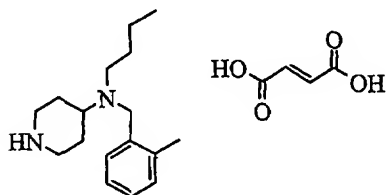
**EXAMPLE 136:**

15 **N-butyl-N-[(2-(difluoromethoxy)phenyl)methyl]piperidin-4-amine fumarate**

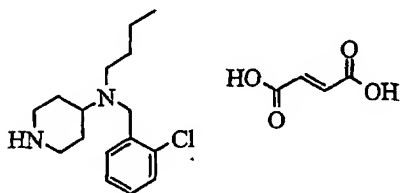


The title product was prepared with 4-(butylamino)piperidine-1-carboxylic acid tert-butyl ester and 2-(difluoromethoxy)benzaldehyde using the method described in example 36(ii). LCMS 12 mins gradient Rt = 2.96 ( $M^+ + 1$ ) 313.1. <sup>1</sup>H NMR (d6-DMSO)  $\delta$  = 7.55 (1H, d), 7.35-7.20 (2H, m) 7.19-7.11 (1H, m), 6.44 (2H, s), 3.62 (2H, s), 3.25 (2H, brd), 2.78-2.65 (3H, m), 2.43-2.40 (2H, m), 1.85-1.61 (4H, m), 1.41-1.15 (4H, m), 0.81-0.70 (3H, m).

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**EXAMPLE 137:****N-butyl-N-[(2-methylphenyl)methyl]piperidin-4-amine fumarate**

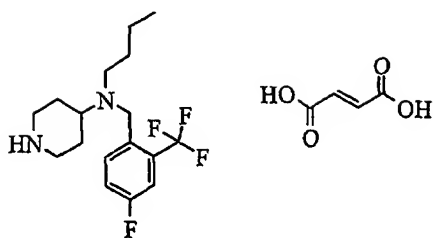
The title product was prepared with 4-(butylamino)piperidine-1-carboxylic acid tert-butyl ester and 2-methylbenzaldehyde using the method described in example 36(ii). LCMS 12 mins gradient Rt = 2.98 ( $M^+ + 1$ ) 261.2.  $^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  = 7.39-7.32 (1H, m), 7.15-7.10 (4H, m), 6.49 (2H, s), 3.55 (2H, s), 3.22 (2H, brd), 2.77-2.65 (3H, m), 2.45-2.39 (2H, m), 2.28 (3H, s, Me), 1.85-1.61 (4H, m), 1.35-1.10 (4H, m), 0.80-0.71 (3H, m)

**EXAMPLE 138:****N-butyl-N-[(2-chlorophenyl)methyl]piperidin-4-amine fumarate**

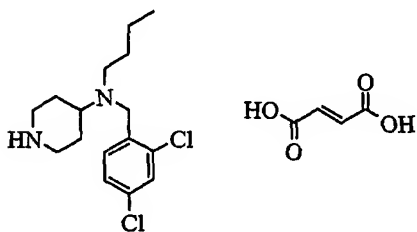
The title product was prepared with 4-(butylamino)piperidine-1-carboxylic acid tert-butyl ester and 2-chlorobenzaldehyde using the method described in example 36(ii). LCMS 12 mins gradient Rt = 3.02 ( $M^+ + 1$ ) 281.2.  $^1\text{H}$  NMR ( $d_6$ -DMSO)  $\delta$  = 7.56 (1H, d, J = 6.03Hz), 7.40-7.23 (3H, m), 6.42 (2H, s), 3.67 (2H, s), 3.25 (2H, brd), 2.79-2.71 (3H, m), 2.49-2.48 (2H, m), 1.84-1.64 (4H, m), 1.31-1.20 (4H, m), 0.81-0.76 (3H, m).

**EXAMPLE 139:****N-butyl-N-[(4-fluoro-2-(trifluoromethyl)phenyl)methyl]piperidin-4-amine fumarate**

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The title product was prepared with 4-(butylamino)piperidine-1-carboxylic acid tert-butyl ester and 4-fluoro-2-(trifluoromethyl)benzaldehyde using the method described in example 36(ii). LCMS 12 mins gradient Rt = 5.30 ( $M^+ + 1$ ) 333.2.  $^1H$  NMR ( $d_6$ -DMSO)  $\delta$  = 7.92-7.88 (1H, m), 7.52-7.49 (2H, m), 6.42 (2H, s), 3.71 (2H, s), 3.25 (2H, brd), 2.79-2.66 (3H, m), 2.49-2.47 (2H, m), 1.85-1.54 (4H, m), 1.41-1.15 (4H, m), 0.81-0.71 (3H, m).

**EXAMPLE 140:****N-butyl-N-[(2,4-dichlorophenyl)methyl]piperidin-4-amine fumarate**

The title product was prepared with 4-(butylamino)piperidine-1-carboxylic acid tert-butyl ester and 2,4-dichlorobenzaldehyde using the method described in example 36(ii). LCMS 12 mins gradient Rt = 4.17 ( $M^+ + 1$ ) 315.1.  $^1H$  NMR ( $d_6$ -DMSO)  $\delta$  = 7.61-7.50 (2H, m), 7.45-7.39 (1H, m), 6.42 (2H, s), 3.67 (2H, s), 3.25 (2H, brd), 2.81-2.59 (3H, m), 2.49-2.48 (2H, m), 1.85-1.55 (4H, m), 1.48-1.15 (4H, m), 0.85-0.75 (3H, m).

15

Examples 141-152 and 157-158 shown in Table 1 below were prepared using a method similar to that described for example 56 using 1,1-dimethylethyl 4-[(2-methylpropyl)amino]piperidine-1-carboxylate and the appropriately substituted benzaldehyde. Examples 153-156 shown in Table 1 below were prepared similarly to method described for example 56 from 1,1-dimethylethyl 4-[(2,3-

20

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dichlorophenyl)methyl]amino}piperidine-1-carboxylate and the appropriately substituted aldehyde.

**1,1-Dimethylethyl 4-[(2,3-dichlorophenyl)methyl]amino}piperidine-1-carboxylate**

- 5 To a solution of N-(*tert*-butoxycarbonyl)-4-piperidone (11.6g, 60mmol, 1eq) and 2,3-dichlorobenzylamine (10.56g, 60mmol, 1eq) in 1,2-dichloroethane (200 ml) was added sodium triacetoxyborohydride (17.8g, 84mmol, 1.4eq) and the reaction mixture stirred for 5 hours. The mixture was diluted with water (100 ml) and 2N sodium hydroxide (140 ml), and then extracted with DCM (3 x 50 ml). The combined organic extracts were  
10 washed with brine (100 ml), dried (MgSO<sub>4</sub>) and the solvent removed *in vacuo* to give a yellow oil 1,1-dimethylethyl 4-[(2,3-dichlorophenyl)methyl]amino}piperidine-1-carboxylate (20.2g, 94%) as a colourless oil; LCMS (6 min): Rt = 3.00 min, (M<sup>+</sup>+1) = 359.1.

15 **1,1-Dimethylethyl 4-[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate**

- The title compound was prepared using a method similar to that described for 1,1-Dimethylethyl 4-[(2,3-dichlorophenyl)methyl]amino}piperidine-1-carboxylate with 4-fluorobenzylamine to give 1,1-dimethylethyl 4-[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (11.18g, 98%) as a colourless solid;  
20 LCMS (12 min): Rt = 2.40 min, (M<sup>+</sup>+1) = 309.4.

**2-Chloro-3-methylbenzaldehyde**

- (i) To a solution of 2-chloro-3-methylbenzoic acid (1g, 5.88 mmol, 1 eq) in dry THF (10 ml) under nitrogen atmosphere at 0°C was added dropwise borane-dimethyl sulphide  
25 complex (0.523 ml, 6.47 mmol, 1.1 eq). After the addition was complete the mixture was heated to reflux for 3 hours, cooled to room temperature and poured slowly into water (100 ml). The aqueous layer was extracted with DCM (5 x 100 ml) and the combined organic layers were dried (MgSO<sub>4</sub>) the solvent was removed *in vacuo* to yield the 2-chloro-3-methylbenzylalcohol (1g, 100%) as a white solid; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ= 7.38-7.11 (3H, m), 4.75 (2H, s) and 2.39 (3H, s).  
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(ii) A solution of DCM (30 ml) was cooled to  $-78^{\circ}\text{C}$  and oxalyl chloride (1.34 ml, 15.2mmol, 1.2eq) was added under nitrogen followed by dropwise addition of DMSO (2.2 ml, 31.7mmol, 2.5eq) in DCM (10ml). After stirring for 15 min a solution of 2-chloro-3-methylbenzylalcohol (2g, 12.7mmol, 1eq) in DCM (12 ml) was added dropwise. After a further 30 min triethylamine (9.03 ml, 63.5mmol, 5eq) was added in one portion and the mixture warmed to room temperature over 1 hour. The reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate (50 ml) and the aqueous layer extracted with DCM (2 x 50 ml). The combined organic extracts were dried ( $\text{MgSO}_4$ ) and the solvent removed *in vacuo* to give 2-chloro-3-methylbenzaldehyde (1.8g, 91.4%) as a yellow oil;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ = 10.53 (1H, s, CHO), 7.81-7.74 (1H, m, ArH), 7.53-7.46 (1H, m, ArH), 7.34-7.23 (1H, m, ArH) and 2.46 (3H, s).

### 3-chloro-2-methylbenzaldehyde

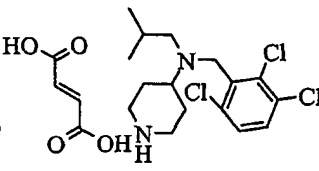
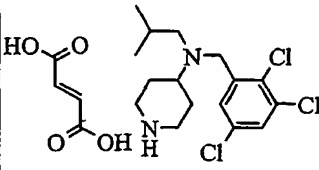
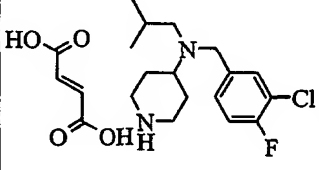
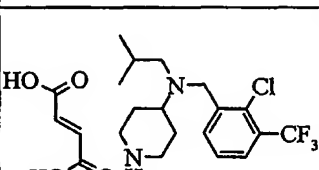
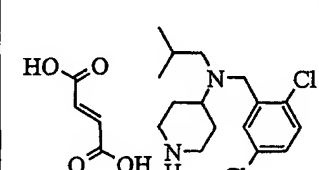
(i) The title compound was prepared using a method similar to that described when synthesising 2-chloro-3-methylbenzaldehyde. Starting with 3-chloro-2-methylbenzoic acid, gave 3-chloro-2-methylbenzylalcohol (10g, 100%) as a white solid;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$ = 7.40-7.05 (3H, m), 4.75-4.62 (2H, m) and 2.35 (3H, s).

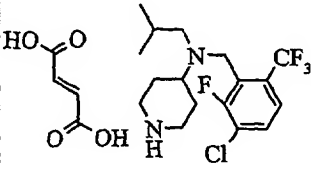
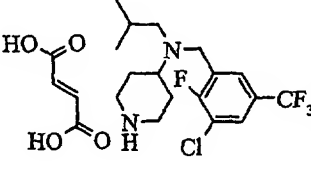
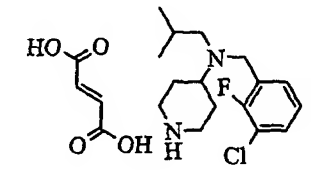
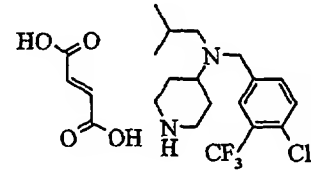
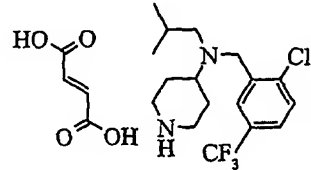
(ii) The title compound was prepared using a method similar to that described when synthesising 2-chloro-3-methylbenzaldehyde. Starting with starting with 3-chloro-2-methylbenzylalcohol, gave 3-chloro-2-methylbenzaldehyde (1.6g, 81.2%) as a yellow oil;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$ = 10.28 (1H, s, CHO), 7.78-7.69 (1H, m, ArH), 7.61-7.55 (1H, m, ArH), 7.35-7.25 (1H, m, ArH) and 2.70 (3H, s).

Table 1

Example No.	Structure	Name	LCMS RT (12 minute), $\text{M}^+ + 1$

-134-

141		N-(2-Methylpropyl)-N-[(2,3,6-trichlorophenyl)methyl]piperidin-4-amine fumarate	5.98 min, 349.0
142		N-(2-Methylpropyl)-N-[(2,3,5-trichlorophenyl)methyl]piperidin-4-amine fumarate	6.35 min, 349.0
143		N-(2-Methylpropyl)-N-[(3-chloro-4-fluorophenyl)methyl]piperidin-4-amine fumarate	4.26 min, 299.1
144		N-(2-Methylpropyl)-N-[(2-chloro-3-(trifluoromethyl)phenyl)methyl]piperidin-4-amine fumarate	5.89 min, 349.1
145		N-(2-Methylpropyl)-N-[(2,5-dichlorophenyl)methyl]piperidin-4-amine fumarate	5.64 min, 315.1

146		N-(2-Methylpropyl)-N-{[3-chloro-2-fluoro-6-(trifluoromethyl))phenyl]methyl}piperidin-4-amine fumarate	6.01 min, 367.1
147		N-(2-Methylpropyl)-N-{[(3-chloro-2-fluoro-5-(trifluoromethyl))phenyl]methyl}piperidin-4-amine fumarate	6.22 min, 367.1.
148		N-(2-Methylpropyl)-N-{[(3-chloro-2-fluoro)phenyl]methyl}piperidin-4-amine fumarate	4.52 min, 299.1
149		N-(2-Methylpropyl)-N-{[(4-chloro-3-(trifluoromethyl))phenyl]methyl}piperidin-4-amine fumarate	5.65 min, 349.1
150		N-(2-Methylpropyl)-N-{[(2-chloro-5-(trifluoromethyl))phenyl]methyl}piperidin-4-amine fumarate	6.06 min, 349.1

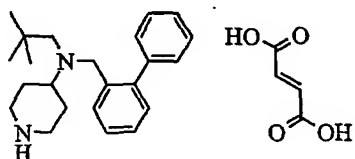
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151		N-(2-Methylpropyl)-N-([(2-chloro-6-fluoro-3-methylphenyl)methyl]piperidin-4-amine fumarate	4.75 min, 313.1
152		N-(2-Methylpropyl)-N-([(6-chloro-2-fluoro-3-methylphenyl)methyl]piperidin-4-amine fumarate	4.71 min, 313.1
153		N-(1-Propyl)-N-([(2,3-dichlorophenyl)methyl]piperidin-4-amine fumarate	3.32 min, 301.1
154		N-(1-Butyl)-N-([(2,3-dichlorophenyl)methyl]piperidin-4-amine fumarate	3.84 min, 315.1
155		N-(Cyclopropylmethyl)-N-([(2,3-dichlorophenyl)methyl]piperidin-4-amine fumarate	3.34 min, 313.1



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156		N-(2,2-dimethylpropyl)-N-([(2,3-dichlorophenyl)methyl]piperidin-4-amine fumarate	6.10 min, 329.1.
157		N-(2-Methylpropyl)-N-([(3-chloro-2-methylphenyl)methyl]piperidin-4-amine fumarate	2.99 min, 295.2
158		N-(2-Methylpropyl)-N-([(2-chloro-3-methylphenyl)methyl]piperidin-4-amine fumarate	3.86 min, 295.2

**EXAMPLE 159:****N-(2,2-Dimethylpropyl)-N-([1,1-biphenyl]-2-yl-methyl)piperidin-4-amine fumarate**

- (i) To 10% Pd/C (1.0g, 10%wt), under nitrogen, was added a solution of the N-(tert-butoxycarbonyl)-4-piperidone (10g, 550.09 mmol, 1.0 eq) and neopentylamine (4.46g, 51.19mmol, 1.02 eq) in ethanol (60 ml). This was hydrogenated for 3 hrs, at 60 psi hydrogen, using a Parr Hydrogenator. The catalyst was removed by filtration through Celite. Solvent was removed under vacuum to give 1,1-dimethylethyl 4-[(2,2-dimethylpropyl)amino]piperidine-1-carboxylate as a colourless, slightly cloudy oil (13.60g, 100%). LCMS: (6 min):  $R_t = 2.6$  min,  $(M^+ + 1) = 271$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 4.00\text{--}3.97$  (2H, m,  $\text{NCH}_2$ ),  $2.86\text{--}2.78$  (2H, m,  $\text{NCH}_2$ ),  $2.58\text{--}2.49$  (1H, m,

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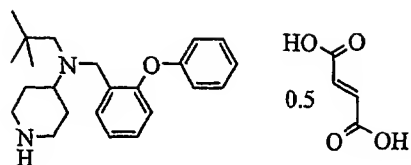
NCH<sub>2</sub>), 2.35 (2H, s, NCH<sub>2</sub>tBu), 1.84-1.78 (2H, m, CCH<sub>2</sub>), 1.45 (9H, s, OC(CH<sub>3</sub>)<sub>3</sub>), 1.31-1.19 (2H, m, CCH<sub>2</sub>), 0.91 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>).

(ii) To a solution of 1,1-dimethylethyl 4-[(2,2-dimethylpropyl)amino]piperidine-1-carboxylate (0.41g, 1.50mmol, 1.0eq), 2-phenylbenzyl bromide (0.133 ml, 1.80 mmol, 1.2eq) in dry acetonitrile (5 ml) was added anhydrous potassium carbonate (0.33g, 2.40mmol, 1.6eq). The mixture was stirred overnight at room temperature. The reaction mixture was concentrated under vacuum to give a white solid. The white solid was taken up in dichloromethane (10 ml) and this washed with water (10 ml). The dichloromethane layer was passed through a hydrophobic frit then diluted with methanol (10 ml). This solution was loaded onto an SCX-2 (10g) column. The column was washed with methanol (50 ml) then basic material was eluted using 2N ammonia in methanol (50 ml). Concentration of the ammonia/methanol solution under vacuum yielded a white solid (0.60g, 93%). To a solution of this oil (0.60g, 1.37mmol, 1.0eq) in dichloromethane (10 ml) was added trifluoroacetic acid (TFA) (1.67 ml, 22.5mmol, 16.4eq). The solution was stirred overnight at room temperature. Solvent and TFA were removed *in vacuo*. The resulting oil was taken up in methanol and loaded onto an SCX-2 (10g) column. The column was washed with methanol (50 ml). Basic material was then eluted using 2N ammonia in methanol (50 ml). Removal of solvent from the ammonia/methanol mixture under vacuum, gave a colourless oil (0.47g, 100%). The oil was taken up in methanol. To this solution was added a solution of fumaric acid (0.16g, 1.40mmol, 1.01eq) in methanol followed by diethyl ether. The resulting precipitate was collected by filtration to give the title compound as a white solid (0.59g, 94%). LCMS: (12 min): Rt = 5.9 min, (M<sup>+</sup>+1) = 337; <sup>1</sup>H NMR (300 MHz, MeOD): δ = 7.81-7.77 (1H, m, ArH), 7.47-7.28 (7H, m, ArH), 7.20-7.15 (1H, m, ArH), 6.70 (3H, s, fumarate CH), 3.71 (2H, s, CH<sub>2</sub>Ar), 3.38-3.27 (2H, m, NCH<sub>2</sub>), 2.79 (2H, dt, NCH<sub>2</sub>), 2.61-2.51 (1H, m, NCH), 2.23 (2H, s, NCH<sub>2</sub>tBu), 1.73-1.49 (4H, m, CCH<sub>2</sub>), 0.85 (9H, s, CH<sub>3</sub>).

**EXAMPLE 160:**

**N-(2,2-Dimethylpropyl)-N-[(2-phenoxyphenyl)methyl]piperidin-4-amine hemifumarate**

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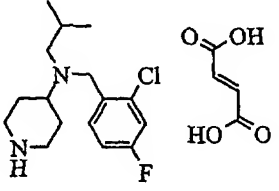
- (i) To a 250ml round bottomed flask was added 3-fluorobenzaldehyde (12.4g, 100mmol, 1.0 eq), phenol (11.3g, 120mmol, 1.2eq), potassium carbonate (16.6g, 120mmol, 1.2eq) and dimethylacetamide (100 ml). The reaction mixture was heated at reflux for 16 hours. The mixture was then diluted with water and extracted with diethyl ether. The combined organic extracts were washed with water (3x) and brine. The washed extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give a yellow oil (15.7g). This was purified by automated flash chromatography using an ISCO Combiflash system (SiO<sub>2</sub> (120g x 2); 0-10% ethyl acetate in cyclohexane gradient elution over 40 minutes) to give 3-phenoxybenzaldehyde as a colourless oil (14.8g, 75%). LCMS: (6 min), Rt = 4.0 min, (M<sup>+</sup>+1) = 199; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ= 10.52 (1H, s, CHO), 7.94 (1H, dd, ArH), 7.54-7.45 (1H, m, ArH), 7.42-7.36 (2H, m, ArH), 7.21-7.15 (2H, m, ArH), 7.09-7.04 (2H, m, ArH), 6.90 (1H, d, ArH).
- (ii) To a solution of 1,1-dimethylethyl 4-[(2,2-dimethylpropyl)amino]piperidine-1-carboxylate (0.41g, 1.50mmol, 1.0eq), as prepared in Example (159), in 1,2-dichloroethane (10 ml) was added 3-phenoxybenzaldehyde (0.89g, 4.50mmol, 3.0 eq). To this was added a solution of sodium triacetoxyborohydride (0.95g, 4.50mmol, 3.0eq) in dimethylformamide (2 ml). This mixture was left to stir under nitrogen, at room temperature, overnight. To the reaction mixture was added water (10 ml) and the mixture stirred vigorously for several minutes. The chlorinated organic layer was run through a hydrophobic frit to remove water, diluted with methanol (10 ml) and loaded onto an SCX-2 (10g) column. The column was washed with methanol (50 ml) then basic material eluted with 2N ammonia in methanol. The ammonia/methanol solution was concentrated *in vacuo* to give 1,1-dimethylethyl 4-[(3-phenoxyphenylmethyl)(2,2-dimethylpropyl)amino]piperidine-1-carboxylate as a colourless oil (0.58g, 74%). To a solution of this oil (0.58g, 1.28 mmol, 1.0eq) in dichloromethane (10ml) was added trifluoroacetic acid (TFA) (1.67 ml, 22.5mmol, 17.6eq). The solution was stirred overnight at room temperature. Solvent and TFA were removed *in vacuo*. The resulting

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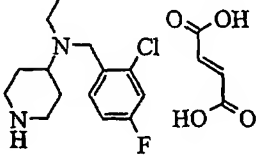
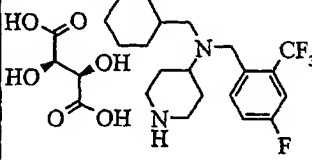
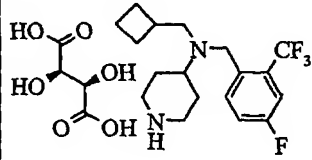
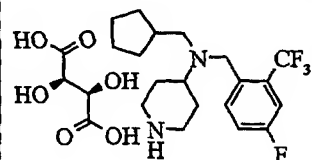
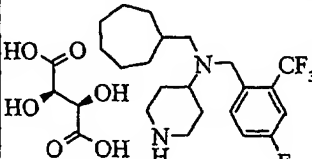
oil was taken up in methanol and loaded onto an SCX-2 (10g) column. The column was washed with methanol (50 ml). Basic material was then eluted using 2N ammonia in methanol (50 ml). Removal of solvent from the ammonia/methanol mixture under vacuum, gave a colourless oil (0.45g, 100%). The oil was taken up in methanol. To this solution was added a solution of fumaric acid (0.16g, 1.33mmol, 1.04eq) in methanol. The mixture was left to stir for a couple of minutes, then, diethyl ether was added. The resulting precipitate was collected by filtration to give the title compound as a white solid (0.396g, 76%). This was recrystallised a second time using the same solvent system to give the hemifumarate salt as a white solid (0.195g, 37%). LCMS: (12 min),  $R_t = 5.4$  min,  $(M^+ + 1) = 353$ ;  $^1H$  NMR (300 MHz, MeOD):  $\delta = 7.76-7.72$  (1H, m, ArH), 7.37-7.19 (4H, m, ArH), 7.11-7.03 (1H, m, ArH), 6.94-6.89 (3H, m, ArH), 6.66 (3H, s, fumarate CH), 3.81 (2H, s,  $CH_2Ar$ ), 3.39 (2H, brd s,  $NCH_2$ ), 2.84-2.63 (3H, m,  $NCH_2$ ,  $NCH$ ), 2.43 (2H, s,  $NCH_2tBu$ ), 1.97-1.93 (2H, m,  $CCH_2$ ), 1.79-1.64 (2H, m,  $CCH_2$ ), 0.86 (9H, s,  $CH_3$ ).

Table 2 examples 161 - 169 were similarly prepared.

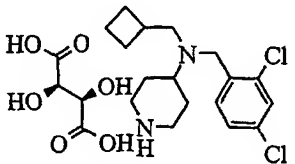
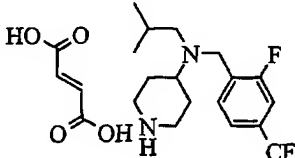
Table 2

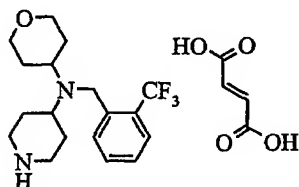
Example No.	Structure	Name	LCMS (12 min or 6 min*), $M^+ + 1$
161		N-(2-Methylpropyl)-N-[(2-chloro-4-fluoro)phenyl]methyl} piperidin-4-amine fumarate	4.32 min, 299.1/301.1

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162		N-(1-Propyl)-N-([(2-chloro-4-fluoro)phenyl]methyl)piperidin-4-amine fumarate	2.63 min, 285.1/287.1
163		N-(Cyclohexylmethyl)-N-([(4-fluoro-2-(trifluoromethyl))phenyl]methyl)piperidin-4-amine L-Tartrate	2.69 min*, 373.3
164		N-(Cyclobutylmethyl)-N-([(4-fluoro-2-(trifluoromethyl))phenyl]methyl)piperidin-4-amine L-Tartrate	1.94 min*, 345.2
165		N-(Cyclopentylmethyl)-N-([(4-fluoro-2-(trifluoromethyl))phenyl]methyl)piperidin-4-amine L-Tartrate	2.43 min*, 359.2
166		N-(Cycloheptylmethyl)-N-([(4-fluoro-2-(trifluoromethyl))phenyl]methyl)piperidin-4-amine L-Tartrate	3.01 min*, 387.3

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167		N-(Cyclobutylmethyl)-N-([(2,4-dichloro-phenyl)]methyl)piperidin-4-amine L-Tartrate	1.46 min*, 327.1
168		N-(2-Methylpropyl)-N-([(2-fluoro-4-(trifluoromethyl))phenyl]methyl)piperidin-4-amine fumarate	5.89 min, 333.1/334.1

**EXAMPLE 169:****N-([(2-Trifluoromethyl)phenyl]methyl)-N-tetrahydro-2H-pyran-4-yl-piperidin-4-amine fumarate**

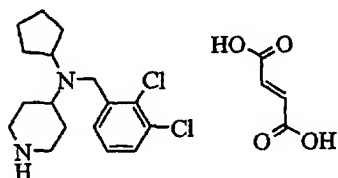
- 5 To a solution of 4-(2H-tetrahydropyran-4-yl)amino-piperidine-1-carboxylic acid tert-butyl ester (0.5g, 1.39mmol, 1.0 eq) in dichloromethane (10 ml) was added the 4-pyranone (0.41g, 4.18mmol, 3.0 eq). To this was added sodium triacetoxyborohydride (0.88g, 4.18mmol, 3.0 eq) and acetic acid (0.08g, 1.39mmol). This mixture was left to stir under nitrogen, at room temperature for 36h. After this time, starting material was still
- 10 evident therefore an additional 3 equivalents of pyranone were added. The reaction mixture was left for a further 16h at room temperature. Starting material was still evident but the reaction was worked up by addition of water (10 ml). The mixture was stirred vigorously for several minutes. The chlorinated organic layer was then run through a hydrophobic frit to remove water. The resulting organic solution was diluted with
- 15 methanol (10 ml) and loaded onto an SCX-2 (10g) column. The column was washed with

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methanol (50 ml) then basic material eluted with 2N ammonia in methanol. The ammonia/methanol solution was concentrated *in vacuo* to give the product. To a solution of this oil (1.0 eq) in dichloromethane (10 ml) was added trifluoroacetic acid (TFA) (15 eq). The solution was stirred at room temperature for 4h. Solvent and TFA were removed  
5 *in vacuo*. The resulting oil was taken up in methanol and loaded onto an SCX-2 (10 g) column. The column was washed with methanol (50 ml). Basic material was then eluted using 2N ammonia in methanol (50 ml). Removal of solvent from the ammonia/methanol mixture under vacuum, gave the desired compounds as an oil.

The oil was taken up in diethyl ether. To this solution was added a solution of fumaric  
10 acid (1 eq) in hot methanol and then cooled. The resulting precipitate was collected by filtration to give the title compound as a white solid (0.065g). LCMS- (12 mins gradient): Rt = 4.69 ( $M^+ + 1$ ) 343.1/344.2;  $^1\text{H}$  NMR (MeOD)  $\delta$  = 7.90 (1H, d), 7.58-7.45 (2H, m), 7.32-7.25 (1H, m), 6.49 (4H, s), 3.90-3.80 (4H, m), 3.35-3.19 (5H, m), 3.15-2.81 (3H, m), 2.80-2.71 (1H, m), 1.95-1.85 (2H, brd), 1.79-1.49 (6H, m).

15

**EXAMPLE 170:****N-(Cyclopentyl)-N-[(2,3-dichlorophenyl)methyl]piperidin-4-amine fumarate**

To a solution of 1,1-dimethylethyl 4-[[[(2,3-dichlorophenyl)methyl]amino]piperidine-1-carboxylate (0.54g, 1.5mmol, 1eq) and cyclopentanone (0.38g, 4.5mmol, 3eq) in 1,2-dichloroethane (10 ml) was added acetic acid (0.09ml, 1.5mmol, 1eq) and sodium triacetoxyborohydride (0.95g, 4.5mmol, 3eq) in dimethylformamide (2 ml). After 16  
20 hours the reaction was incomplete so a further portion of cyclopentanone (0.38g, 4.5 mmol, 3eq) was added and the mixture stirred for 16 hours. No further reaction was observed so additional portions of cyclopentanone (0.38g, 4.5mmol, 3eq), acetic acid  
25 (0.09 ml, 1.5mmol, 1eq) and sodium triacetoxyborohydride (0.95g, 4.5mmol, 3eq) were added and left to stir for 48 hours. The reaction was quenched with water (5 ml) and 2N NaOH (5 ml), and the organic layer separated by passing through a hydrophobic frit.

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This was diluted with methanol (10 ml) and loaded onto a SCX-2 ion exchange cartridge (5g) washed with methanol (15 ml) and the product eluted with 2M ammonia in methanol solution (15 ml). The solvent removed *in vacuo* to give an oil which was purified by automated flash chromatography using an ISCO Combiflash system (40g SiO<sub>2</sub>) with a  
5 gradient of 0-30% ethyl acetate in *iso*-hexane over 40 minutes to give 1,1-dimethylethyl 4-[[[(2,3-dichlorophenyl)methyl](cyclopentyl)amino]-piperidine-1-carboxylate as a colourless oil. To this oil was added a solution of anisole (1.4 ml) and trifluoroacetic acid (1.4 ml, 18.3mmol, 12eq), in DCM (7 ml) and the mixture stirred at room temperature for 16 hrs. The solvent removed *in vacuo* and the residue diluted with methanol (5 ml) and  
10 loaded onto SCX-2 ion exchange cartridge (5g). The column was washed with methanol (15 ml) and the product eluted with 2M ammonia in methanol solution (15 ml) the solvent removed *in vacuo* to give (282mg, 86%) as a colourless oil. The product was taken up in diethyl ether (15 ml) and a few drops of methanol were added to solubilize. A hot solution of fumaric acid (99.9mg, 1.0mmol, 1 eq) in methanol (1ml) was added and the  
15 solution was heated adding a few drops of methanol added until all solid was in solution, then the mixture was allowed to slowly cool to 0°C. The product was collected by filtration and dried in a vacuum oven (40°C for 2 hrs) to give N-(Cyclopentyl)-N-[[[(2,3-dichloro)phenyl]methyl]piperidin-4-amine fumarate (282 mg, 64%) as a white solid. LCMS (12 min): Rt = 4.38 min, (M<sup>+</sup>+1) = 327.1; <sup>1</sup>H NMR (300 MHz, MeOD): δ= 7.62-  
20 7.59 (1H, m, ArH), 7.30-7.27 (1H, m, ArH), 7.17 (1H, t, J = 7.8, ArH), 6.58 (2H, s, fumarate CH), 3.74 (2H, s, CH<sub>2</sub>Ar) 3.32-3.20 (3H, m, NCH), 2.95-2.80 (3H, m, NCH), 1.91 (2H, br d, J = 13.8, CH<sub>2</sub>), 1.71-1.28 (10H, m, CH<sub>2</sub>).

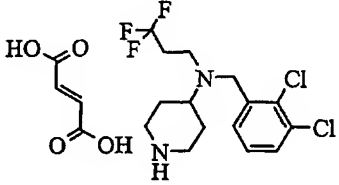
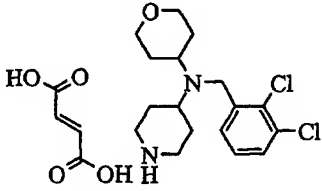
Examples 171-172 shown in table 3 were prepared using a method similar to that  
25 described for example 170 starting from 1,1-dimethylethyl 4-[[[(2,3-dichlorophenyl)methyl]amino]piperidine-1-carboxylate and the appropriately substituted aldehyde or ketone. For example (172) the fumarate salt was recrystallised from methanol and ether to purify.

30 Table 3 examples 171 – 172 were similarly prepared.



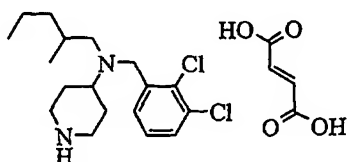
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Table 3

Example No.	Structure	Name	LCMS (12 minute) $M^+ + 1$
171		N-(3,3,3-Trifluoropropyl)-N- {[(2,3-dichloro)phenyl]methyl}piperidin-4-amine fumarate	3.53 min, 355.1
172		N-([(2,3-dichloro)phenyl]methyl)-N-tetrahydro-2H-pyran-4-yl-piperidin-4-amine fumarate	4.53 min, 343

**EXAMPLE 173:**

5 **N-(2-Methylpentyl)-N-([(2,3 dichloro)phenyl]methyl)piperidin-4-amine fumarate-isomer 1**



Prepared using a method similar to that described for example 141 starting with 1,1-dimethylethyl 4-([(2,3-dichlorophenyl)methyl]amino}piperidine-1-carboxylate and 2-methylvaleraldehyde. Before formation of the fumarate salt the racemic mixture was

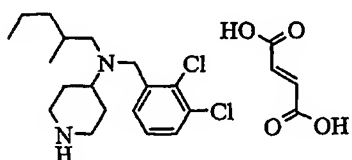
10 separated into their two enantiomers by chiral chromatography on a Chiralcel OD(3641) using 50% Heptane/ 50% ethanol and 0.2% DMEA as the mobile phase at a rate of 0.5 ml/min. To a solution of the free base of the first eluting enantiomer (201 mg, 0.5 mmol,

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1 eq) in diethyl ether (10 ml) and a few drops of methanol were added to solubilize. A hot solution of fumaric acid (60 mg, 0.5 mmol, 1 eq) in methanol (1 ml) was added and the solution was heated adding a few drops of methanol added until all solid was in solution, then the mixture was allowed to slowly cool to 0°C. The product was collected  
 5 by filtration and dried in a vacuum oven (40°C for 2 hrs) to give N-(2-Methylpentyl)-N-[(2,3-dichlorophenyl)methyl]piperidin-4-amine fumarate isomer 1 (173 mg, 25.1%).  
 LCMS (12 min): Rt = 6.14 min, (M<sup>+</sup>+1) = 343.1; <sup>1</sup>H NMR (300 MHz, MeOD): δ= 7.45-7.42 (1H, m, ArH), 7.32 (1H, dd, J = 1.6 and 8.0, ArH), 7.17 (1H, t, J = 8.0, ArH), 6.58 (2H, s, fumarate CH), 3.71 (2H, s, CH<sub>2</sub>Ar) 3.40-3.22 (2H, m, NCH), 2.88-2.80 (2H, m,  
 10 NCH), 2.75-2.67 (1H, m, NCH), 2.33 (1H, dd, J = 12.8 and 6.6, CH), 2.19-2.16 (1H, dd, J = 12.8 and 7.3, CH), 2.02-1.91 (2H, m, CH<sub>2</sub>), 1.77-1.62 (2H, m, CH<sub>2</sub>), 1.34-1.05 (4H, m, CH<sub>2</sub>), 0.91-0.79 (1H, m, CH) and 0.76-0.72 (6H, m, 2 x CH<sub>3</sub>).

**EXAMPLE 174:**

15 **N-(2-Methylpentyl)-N-[(2,3 dichloro)phenyl)methyl]piperidin-4-amine fumarate-isomer 2**

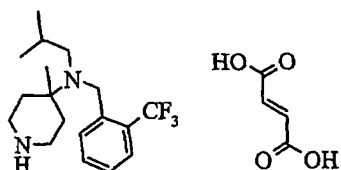


Prepared using a method similar to that described for example (173) taking the free base of the second eluting enantiomer (211mg, 0.6mmol, 1eq) and forming the fumarate salt to give N-(2-Methylpentyl)-N-[(2,3-dichlorophenyl)methyl]piperidin-4-amine fumarate  
 20 isomer 2 (215 mg, 31.2%). LCMS (12 min): Rt = 6.14 min, (M<sup>+</sup>+1)= 343.1; <sup>1</sup>H NMR (300 MHz, MeOD): δ= 7.45-7.42 (1H, m, ArH), 7.32 (1H, dd, J = 1.6 and 8.0, ArH), 7.17 (1H, t, J = 8.0, ArH), 6.58 (2H, s, fumarate CH), 3.71 (2H, s, CH<sub>2</sub>Ar) 3.40-3.22 (2H, m, NCH), 2.88-2.80 (2H, m, NCH), 2.75-2.67 (1H, m, NCH), 2.33 (1H, dd, J = 12.8 and 6.6, CH), 2.19-2.16 (1H, dd, J = 12.8 and 7.3, CH), 2.02-1.91 (2H, m, CH<sub>2</sub>), 1.77-1.62 (2H, m,  
 25 CH<sub>2</sub>), 1.34-1.05 (4H, m, CH<sub>2</sub>), 0.91-0.79 (1H, m, CH) and 0.76-0.72 (6H, m, 2 x CH<sub>3</sub>).

**EXAMPLE 175:**

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**N-(2-Methylpropyl)-4-methyl-N-[(2-(trifluoromethyl)phenyl)methyl]piperidin-4-amine fumarate**



- (i) To a stirred solution of 1-benzyl-4-piperidone (10.0g, 52.84mmol) in dry diethyl ether (100 ml) cooled to  $-78^{\circ}\text{C}$  under a nitrogen atmosphere, was added a solution of methyl lithium in diethyl ether (1.6M, 46.2 ml) dropwise. After addition, stirred at  $-78^{\circ}\text{C}$  for 1.5h then quenched the reaction by addition of water. After warming to room temperature, the organic phase was separated and the aqueous phase washed with diethyl ether (3x). The combined organic phases was washed with brine, dried over magnesium sulphate, filtered and evaporated to an oil (11.1g). The crude oil was purified using an ISCO combiflash on a 120g cartridge eluting with ethyl acetate to remove starting material and then gradient elution with ethyl acetate-methanol 0 to 12% over 35min. 1-benzyl-4-hydroxy-4-methylpiperidine was obtained as a pale yellow oil (5.64g).
- (ii) To a stirred solution of 1-benzyl-4-hydroxy-4-methylpiperidine (5.63g, 27.42mmol) in isobutyronitrile (30ml) cooled to  $5^{\circ}\text{C}$  was added conc. sulphuric acid (25 ml) dropwise. After addition, the suspension was stirred at room temperature overnight. The clear solution was cooled to  $5^{\circ}\text{C}$  and adjusted to a pH of 9.2 by dropwise addition of 50% aqueous sodium hydroxide (50 ml) followed by aqueous sodium carbonate. The mixture was extracted with dichloromethane (3x) and the extracts washed with water (3x) and brine. The organic phase was dried over magnesium sulphate, filtered and evaporated. The brown oil was dried under vacuum to give the 1-benzyl-4-isopropylcarboxamido-4-methylpiperidine (0.6g).
- (iii) To a stirred suspension of 1-benzyl-4-isopropylcarboxamido-4-methylpiperidine (2.03g, 7.41g), and polymer supported Hunig's base (7.97g, 29.64mmol) in dichloromethane (30ml) at room temperature was added  $\alpha$ -chloroethyl chloroformate (3.18g, 22.23mmol). After stirring at room temperature for 4h, filtered and evaporated. The oil was stirred in methanol (20 ml) overnight at room temperature. Diluted with methanol (40ml) and added powdered SCX-2, after stirring for 0.5h, filtered and washed

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powder with 2 volumes of methanol and then eluted with 3 volumes of methanolic ammonia. Evaporation gave an oil (0.52g).

The oil was dissolved in dichloromethane (10ml) and triethylamine (418mg, 4.14mmol), a catalytic amount of 4-dimethylaminopyridine and a solution of di-t-butyl dicarbonate in tetrahydrofuran (1.0M, 3.86 ml) added. The solution was stirred at room temperature for 1.5h then diluted with dichloromethane, washed with water (2x), aqueous 2M HCl, water and brine. Dried over magnesium sulphate, filtered and evaporated to give 1-butoxycarbonyl-4-(2-methylpropyl)carboxamido-4-methylpiperidine as an oil (0.68g).

(iv) To a stirred solution of 1-butoxycarbonyl-4-isopropylcarboxamido-4-methylpiperidine (665mg, 2.35mmol) in dry tetrahydrofuran (10 ml) at room temperature under a nitrogen atmosphere was added a solution of borane in tetrahydrofuran (1.0M, 4.7 ml). The reaction mixture was heated at reflux for 1.5h then cooled to 5°C and aqueous 5M HCl (0.6ml) added. After stirring at 5°C for 10min, aqueous NaOH was added until reaction mixture was basic and then extracted with diethyl ether (2x). Extracts were washed with water (2x) and brine, dried over magnesium sulphate, filtered and evaporated to an oil. Purified on a CBA column (10g) eluting with methanol and the methanolic ammonia to give 1-butoxycarbonyl-4-isobutylamino-4-methylpiperidine as a colourless oil (0.19g).

(v) To a stirred suspension of 1-butoxycarbonyl-4-isobutylamino-4-methylpiperidine (188mg, 0.70mmol) and anhydrous potassium carbonate (125mg, 0.90mmol) in dry acetonitrile at room temperature under an atmosphere of nitrogen was added 2-trifluoromethylbenzyl bromide (200mg, 0.84mmol). The suspension was heated at reflux for 3 days, cooled to room temperature and filtered. Washed solids with methanol and the filtrate added to an SCX-2 column (10g). After elution with methanol, elution with methanolic ammonia gave a mixture of required product 1-butoxycarbonyl-4-methyl-4-{N-(2-methylpropyl)-N-[(2-trifluoromethylphenyl)methyl]}-piperidin-4-amine and starting material in a 11 to 4 ratio as a colourless oil (0.23g). The mixture was taken on to the next step.

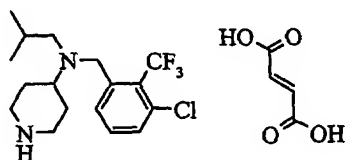
(vi) To a stirred solution of 1-butoxycarbonyl-4-methyl-4-{N-(2-methylpropyl)-N-[(2-trifluoromethylphenyl)methyl]}-piperidin-4-amine and 1-butoxycarbonyl-4-isobutylamino-4-methylpiperidine (0.23g) in dichloromethane (10 ml) at room

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temperature was added trifluoroacetic acid (0.41 ml, 5.30mmol) Stirred at room temperature overnight and then evaporated. The resulting oil was dissolved in methanol and purified on SCX-2 column (5g) eluting with methanol and methanolic ammonia to give a colourless oil (0.16g). This mixture was then separated by preparative lcms to give the title product as its acetate salt. This was converted to its free base by passing down an SCX-2 column to give a colourless oil (96mg). The oil was dissolved in diethyl ether and a hot solution of fumaric acid (34mg) added. The resulting colourless crystals were filtered, washed with diethyl ether and dried *in vacuo* at 50°C to give the title product (112mg). <sup>1</sup>HNMR (CD<sub>3</sub>OD): δ= 8.15 (1H, d), 7.67-7.59 (2H, m), 7.40 (1H, t), 6.70 (2H, s), 3.98 (2H, s), 3.32-3.24 (2H, m), 3.09-2.97 (2H, m), 2.48 (2H, d), 2.00-1.76 (4H, m), 1.43-1.32 (1H, m), 1.22 (3H, s), 0.92 (6H, d); LCMS 5.83min [M<sup>+</sup>+H]: 329.

**EXAMPLE 176:**

**N-(2-Methylpropyl)-N-[(3-chloro-2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine fumarate**



- (i) To a solution of 1-chloro-3-methyl-2-(trifluoromethyl)benzene (2g, 13.5mmol, 1 eq) and *N*-bromosuccinimide (2.40g, 13.5mmol, 1eq) in carbon tetrachloride (10 ml) was added a catalytic amount of dibenzoyl peroxide (16mg, 0.7mmol, 0.05 eq) and this was heated to reflux for 6 hours. The reaction mixture was cooled, water (10 ml) and DCM (10 ml) was added. The aqueous layer was separated and extracted with DCM (2 x 10 ml). The combined organic extracts were dried (MgSO<sub>4</sub>) and the solvent removed *in vacuo*. The oil was purified by automated flash chromatography using an ISCO Combiflash system (120 g SiO<sub>2</sub>) with a gradient of 0-40% ether in *iso*-hexane over 40 minutes to give 2-(trifluoromethyl)-3-chlorobenzylbromide (1.55g, 50.6%); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ= 7.60 (3H, m, ArH) and 4.55 (2H, s, CH<sub>2</sub>Br).
- (ii) To a solution of 2-(trifluoromethyl)-3-chlorobenzylbromide (1.35g, 4.9mmol, 2.4 eq) and 1,1-dimethylethyl 4-[(2-methylpropyl)amino]piperidine-1-carboxylate (0.527g,

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2.0mmol, 1 eq) in acetonitrile (25 ml) was added potassium carbonate (0.44g, 3.2mmol, 1.6 eq). The mixture was heated to reflux for 16 hours, the solution was cooled, filtered and the solvent removed *in vacuo*. The oil was purified by automated flash chromatography using an ISCO Combiflash system (40g SiO<sub>2</sub>) with a gradient of 0-20% ethyl acetate in *iso*-hexane over 40 minutes to give 1,1-dimethylethyl 4-[[2-(trifluoromethyl)-3-chlorophenyl]methyl](2-methylpropyl)amino]-piperidine-1-carboxylate (0.89g, 40.7%) as an oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ= 7.92-7.90 (1 H, m, ArH), 7.41-7.35 (2H, m, ArH), 4.16-4.09 (2H, m), 3.83-3.83 (2 H, m, CH<sub>2</sub>Ar), 2.61-2.42 (3H, m), 2.24 (2 H, d, J = 7.2, CH<sub>2</sub>), 1.75-1.66 (2H, m), 1.63-1.51 (1H, m), 1.45-1.36 (11H, m) and 0.85 (6 H, d, J = 6.8, 2 x CH<sub>3</sub>).

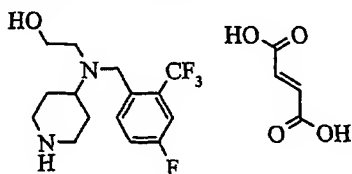
(iii) To a solution of 1,1-dimethylethyl 4-[[2-(trifluoromethyl)-3-chlorophenyl]methyl](2-methylpropyl)amino]-piperidine-1-carboxylate (0.90g, 2.0 mmol, 1eq) in DCM (3 ml) was added trifluoroacetic acid (1. ml, 20.0mmol, 10 eq) and the mixture stirred at room temperature for 16 hr. The solvent removed *in vacuo* and the residue diluted with methanol (10 ml) and loaded onto SCX-2 ion exchange cartridge (10g). The column was washed with methanol (50 ml) and the product eluted with 2M ammonia in methanol solution (50 ml) the solvent removed *in vacuo* to give a colourless oil. The product (0.41mg, 59%) was taken up in diethyl ether (15 ml) and a few drops of methanol were added to solubilize. A hot solution of fumaric acid (137mg, 1.2mmol, 1eq) in methanol (1 ml) was added and the solution was heated adding a few drops of methanol added until all solid was in solution, then the mixture was allowed to slowly cool to 0°C. The product was collected by filtration and dried in a vacuum oven (40°C for 2 hr) to give N-(2-Methylpropyl)-N-[[3-chloro-2-(trifluoromethyl)phenyl]methyl]piperidin-4-amine fumarate (405mg, 43%) as a white solid. LCMS (12 min): Rt = 5.99 min, (M<sup>+</sup>+1) = 349.1. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ= 7.79 (1 H, d, J = 6.9, ArH) 7.44-7.37 (2H, m, ArH), 6.58 (2H, s, fumarate CH), 3.81-3.80 (2 H, m, CH<sub>2</sub>Ar), 3.40-3.31 (2 H, m), 2.88-2.78 (2 H, m), 2.73-2.63 (1 H, m), 2.20 (2 H, d, J = 7.2, CH<sub>2</sub>), 1.95-1.90 (2H, m), 1.73-1.58 (2H, m), 1.50-1.37 (1 H, m) and 0.75 (6 H, d, J = 6.6, 2 x CH<sub>3</sub>).

30

**EXAMPLE 177:**

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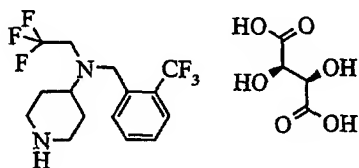
**N-(2-Hydroxyethyl)-N-(((4-fluoro-2-(trifluoromethyl))phenyl)methyl)piperidin-4-amine fumarate**



- (i) To 10% Pd/C (0.5g, 10%wt), under nitrogen, was added a solution of the N-(tert-butoxycarbonyl)-4-piperidone (5g, 25mmol, 1.0eq) and ethanolamine (1.83g, 30mmol, 1.2eq) in ethanol (50 ml). This was hydrogenated for 1.5 hrs, at 65 psi hydrogen, using a PARR hydrogenator. The catalyst was removed by filtration through Celite. Solvent was removed under vacuum to give the secondary amine as a colourless oil (6.4g, 100%) with >98% purity. LCMS (6 mins gradient): Rt = 1.87 (M<sup>+</sup>+1) 267.4.
- (ii) To a solution of amine prepared in initial step (2.0g, 8.19mmol, 1.0eq) in dichloroethane (20 ml) was added the 4-fluoro, 2-(trifluoromethyl)benzaldehyde (2.34g, 12.2mmol, 1.5eq). To this was added sodium triacetoxyborohydride (2.58g, 12.2mmol, 1.5eq.) in DMF (1ml). This mixture was left to stir under nitrogen, at room temperature for 16h. The reaction was worked up by addition of water (10 ml). The mixture was stirred vigorously for several minutes. The chlorinated organic layer was then run through a hydrophobic frit to remove water. The resulting organic solution was diluted with methanol (10 ml) and loaded onto an SCX-2 (10g) column. The column was washed with methanol (50 ml) then basic material eluted with 2N ammonia in methanol. The ammonia/methanol solution was concentrated *in vacuo* to give an oil. This was further purified using ISCO chromatography, eluting with 0-40% ethyl acetate: iso-hexane ramp over 40 min to give the desired compound (0.173g), which was taken onto the next step. To a solution of this oil (1.0eq) in dichloromethane (10 ml) was added trifluoroacetic acid (TFA) (15eq). The solution was stirred at room temperature for 4h. Solvent and TFA were removed *in vacuo*. The resulting oil was taken up in methanol and loaded onto an SCX-2 (10 g) column. The column was washed with methanol (50 ml). Basic material was then eluted using 2N ammonia in methanol (50 ml). Removal of solvent from the ammonia/methanol mixture under vacuum, gave the desired compound as an oil.

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The oil was taken up in diethyl ether. To this solution was added a solution of fumaric acid (1eq) in hot methanol and then cooled. The resulting precipitate was collected by filtration to give the title compound as a white solid (0.43g); <sup>1</sup>HNMR (MeOD) δ= 8.10-8.0 (1H, m), 7.45-7.33 (2H, m), 6.69 (2H, s), 3.91 (2H, s), 3.59-3.41 (4H, m), 3.30-3.21 (1H, s), 3.10-2.81 (3H, m), 2.75-2.68 (2H, m), 2.15 (2H, brd), 1.87-1.70 (2H, m).

**EXAMPLE 178:****N-(2,2,2-Trifluoroethyl)-N-{[(2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine L-Tartrate**

- 10 (i) To a solution of 1,1-dimethylethyl 4-([2-(trifluoromethyl)phenyl]methyl)amino)piperidine-1-carboxylate (0.5g, 1.4mmol, 1 eq) in DCM (10 ml) was added triethylamine (0.40 ml, 2.8mmol, 2 eq), trifluoroacetic anhydride (0.24 ml, 1.7mmol, 1.2eq) and 4-(dimethylamino)pyridine (0.086g, 0.7mmol, 0.5eq). This was stirred at room temperature for 16 hours then quenched with saturated aqueous sodium hydrogen carbonate. The separated aqueous layer was extracted with DCM (3 x 20 ml), the combined organic layers were dried (MgSO<sub>4</sub>) and the solvent removed *in vacuo* to give a colourless oil. This was purified by automated flash chromatography using an ISCO Combiflash system (40g SiO<sub>2</sub>) with a gradient of 20-60% ethyl acetate in *iso*-hexane over 40 minutes to give 1,1-dimethylethyl 4-([2-(trifluoromethyl)phenyl]methyl)(2,2,2-trifluoroacetyl)amino]-piperidine-1-carboxylate (518 mg, 81%). LCMS (6 min): Rt = 4.95 min, (M<sup>+</sup>+23) = 477.42.
- 15 (ii) To a solution of 1,1-dimethylethyl 4-([2-(trifluoromethyl)phenyl]methyl)(2,2,2-trifluoroacetyl)amino]-piperidine-1-carboxylate (518mg, 1.1 mmol, 1eq) in THF (2.5 ml) at 0°C was added dropwise neat borane-tetrahydrofuran complex (0.32 ml, 3.3mmol, 3eq). The reaction mixture was heated to 55°C for 1.5 hr then cooled and quenched with saturated sodium hydrogen carbonate (exothermic). The aqueous layer was separated and extracted with DCM (3 x 20 ml), the combined organic layers were dried (MgSO<sub>4</sub>) and
- 20
- 25



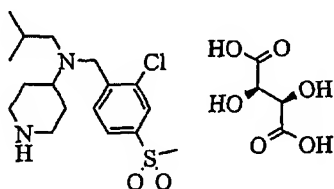
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the solvent removed *in vacuo* to give 1,1-dimethylethyl-4-[[2-(trifluoromethyl)phenyl]methyl}(2,2,2-trifluoroethyl)amino]-piperidine-1-carboxylate (0.353g, 70%) as a white solid. LCMS (6 min):  $R_t = 3.42$  min,  $(M^+ + 1) = 441.4$ .

- (iii) To a solution of 1,1-dimethylethyl 4-[[2-(trifluoromethyl)phenyl]methyl}(2,2,2-trifluoroethyl)amino]-piperidine-1-carboxylate in DCM (2 ml) was added trifluoroacetic acid (0.62 ml, 8mmol, 10eq) and the mixture stirred at room temperature for 16 h. The solvent removed *in vacuo* and the residue diluted with methanol (5 ml) and loaded onto SCX-2 ion exchange cartridge (5g). The column was washed with methanol (15ml) and the product eluted with 2M ammonia in methanol solution (15 ml) the solvent removed *in vacuo* to give an oil which was purified by mass guided preparative LCMS followed by repeat SCX-2 treatment to give a colourless oil. This was taken up in hot methanol (1.5 ml) and added to L-tartaric acid (105mg, 1eq), diethyl ether was added slowly until crystallization occurred. After 16 hours the crystals were collected by filtration and dried in a vacuum oven at 40°C for 8h to give N-(2,2,2-trifluoroethyl)-N-[[2-(trifluoromethyl)phenyl]methyl]piperidin-4-amine-L-Tartrate (154 mg, 39%) as a colourless solid. LCMS (12 min):  $R_t = 5.05$  min,  $(M^+ + 1) = 341.1$ ;  $^1\text{H NMR}$  (300 MHz, MeOD):  $\delta = 7.81$  (1H, d,  $J = 7.9$ , ArH), 7.58-7.49 (2H, m, ArH), 7.34-7.30 (1H, t,  $J = 7.5$ , ArH), 4.30 (2H, s, tartrate CH), 4.01 (2H, s,  $\text{CH}_2\text{Ar}$ ), 3.36-3.25 (4H, m,  $\text{NCH}_2$ ), 2.83-2.69 (3H, m, NCH and  $\text{NCH}_2$ ), 1.94 (2H, d,  $J = 13.0$  Hz), 1.72-1.64 (2H, m,  $\text{CCH}_2$ ).

#### EXAMPLE 179:

#### N-(2-Methylpropyl)-N-[[2-chloro-4-(methylsulfonyl)phenyl]methyl]-piperidin-4-amine L-Tartrate



- (i) 2-Chloro-4-fluorobenzaldehyde (5g, 31.5mmol, 1eq) and methanesulphinic acid sodium salt (3.5g, 34.7mmol, 1.1eq) were dissolved in dry DMSO (30 ml) and heated to 100°C for 16hrs. The mixture was cooled and poured onto crushed ice (50g). After ice

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had melted the solid was filtered and dried in a vacuum oven at 50°C for 2 hours to give 2-chloro 4-(methylsulphonyl)benzaldehyde (4.85g, 70%) as a colourless solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 10.52 (1H, s, CHO), 8.16-7.91 (3H, m, ArH) and 3.10 (3H, s, CH<sub>3</sub>). GCMS: Rt = 7.63 min, (M<sup>+</sup>) = 218.

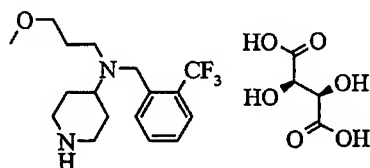
- 5 (ii) To a solution of 1,1-dimethylethyl 4-[(2-methylpropyl)amino]piperidine-1-carboxylate (0.38g, 1.5mmol, 1eq) and 2-chloro 4-(methylsulphonyl)benzaldehyde (984mg, 4.5mmol, 3eq) in THF (10 ml) was added sodium triacetoxyborohydride (0.95g, 4.5mmol, 3eq) and the mixture left to stir for 16h. The reaction was quenched with water (10 ml), then 2N aqueous sodium hydroxide (10 ml), the aqueous layer was separated and  
10 extracted with ethyl acetate (2 x 20 ml). The combined organic layers were washed with brine (20 ml), dried (MgSO<sub>4</sub>) and the solvent removed *in vacuo*. This was diluted with methanol (10 ml) and loaded onto a SCX-2 ion exchange cartridge (5g) washed with methanol (15 ml) and the product eluted with 2M ammonia in methanol solution (15 ml). The solvent removed *in vacuo* to give an oil which was purified by automated flash  
15 chromatography using an ISCO Combiflash system (40g SiO<sub>2</sub>) with a gradient of 0-40% ethyl acetate in iso-hexane over 40 minutes to give 1,1-dimethylethyl 4-[[2-chloro-4-(methylsulphonyl)phenyl]methyl](2-methylpropyl)amino]-piperidine-1-carboxylate (0.45g, 75%) as a colourless oil. This was taken up in DCM (2 ml) and trifluoroacetic acid (1.0 ml, 13.1mmol, 15 eq) was added, the mixture stirred at room temperature for  
20 16h. The solvent removed *in vacuo* and the residue diluted with methanol (5 ml) and loaded onto SCX-2 ion exchange cartridge (5g). The column was washed with methanol (15 ml) and the product eluted with 2M ammonia in methanol solution (15 ml) the solvent removed *in vacuo* to give a colourless oil (320mg, 100%). This was taken up in hot methanol (1.5 ml) and added to L-tartaric acid (105mg, 1eq), diethyl ether was added  
25 slowly until crystallization occurred. After 16 hours the crystals were collected by filtration and dried in a vacuum oven at 40°C for 8 hours to give N-(2-Methylpropyl)-N{[2-chloro-4-(methylsulfonyl)phenyl]methyl}-piperidin-4-amine L-Tartrate (302mg, 66%) as a colourless solid. LCMS (12 min): Rt = 4.25 min, (M<sup>+</sup>+1) = 359.1; <sup>1</sup>H NMR (300 MHz, MeOD): δ = 7.95-7.87 (3H, m, ArH), 4.41 (2H, s, tartrate CH), 3.89 (2H, s, CH<sub>2</sub>Ar), 3.54-3.39 (2H, m, NCH<sub>2</sub>), 3.32 (3H, s, CH<sub>3</sub>), 2.99-2.78 (3H, m, NCH, NCH<sub>2</sub>),  
30

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2.38 (2H, d,  $J = 7.1$ ,  $\text{NCH}_2$ ), 2.06 (2H, br d,  $J = 13.4$ ,  $\text{CCH}_2$ ), 1.89-1.61 (3H, m,  $\text{CCH}_2$  and  $\text{CH}(\text{CH}_3)_2$ ) and 0.89 (6H, d,  $J = 6.6$  Hz,  $2 \times \text{CH}_3$ ).

**EXAMPLE 180:**

5 **N-(3-Methoxypropyl)-N-{[(2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine-L-Tartrate**



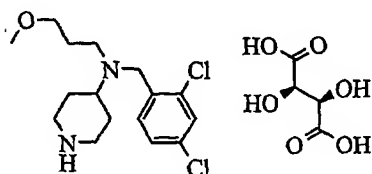
- (i) A solution of N-butoxycarbonyl-4-piperidone (20.0g, 0.10mol) and 3-methoxypropylamine (13.4g, 0.15mol) in ethanol (120ml) was hydrogenated at 60psi over 10% palladium-carbon (2g) for 3h. The catalyst was removed by filtration through celite and the filtrate evaporated to 1-butoxycarbonyl-N-(3-methoxypropyl)piperidin-4-amine as a colourless oil.
- 10 (ii) To a stirred solution of 1-butoxycarbonyl-N-(3-methoxypropyl)piperidin-4-amine (0.50g, 1.84mmol) and 2-trifluoromethylbenzaldehyde (0.64g, 3.67mmol) in dry tetrahydrofuran (10 ml) at room temperature was added sodium triacetoxymethylborohydride (0.97g, 4.60mmol). Aq. saturated sodium bicarbonate was added followed by dichloromethane (15 ml). After stirring for 5min, the organic phase was isolated using a phase separator and evaporated to give a crude oil. Purified on a 40g cartridge of silica using an ISCO combiflash by gradient elution with iso-hexane-ethyl acetate (10 to 40%) to give the required product 1-butoxycarbonyl-N-(3-methoxypropyl)-N-{[(2-
- 20 (trifluoromethyl))phenyl]methyl}piperidin-4-amine contaminated with 2-trifluoromethylbenzyl alcohol as a colourless oil. Taken on to next step without further purification.
- (iii) A solution of 1-Butoxycarbonyl-N-(3-methoxypropyl)-N-{[(2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine (0.72g) in dichloromethane (10ml)
- 25 was stirred at room temperature with trifluoroacetic acid (1.29ml) overnight. The reaction mixture was evaporated and the resulting oil was dissolved in methanol and purified on SCX-2 column (5g) eluting with methanol and methanolic ammonia to give a colourless

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oil (290mg). The oil was dissolved in methanol and L-tartaric acid (132mg) added, warmed to give a clear solution then allowed to stand with vapour of diethyl ether. The crystals were filtered, washed with diethyl ether and dried *in vacuo* at 60°C to give the title product as a colourless solid (347mg). <sup>1</sup>NMR (d<sup>6</sup>-DMSO): δ= 7.90 (1H, d), 7.70-7.64 (2H, m), 7.47 (1H, t), 3.88 (2H, s), 3.79 (2H, s), 3.34-3.23 (4H, m), 3.17 (3H, s), 2.88-2.70 (3H, m), 2.57-2.50 (2H, m), 1.88-1.77 (2H, m), 1.76-1.50 (4H, m). LCMS 3.69min. [M+H]: 331.

**EXAMPLE 181:**

10 **N-(3-Methoxypropyl)-N-{[(2,4-dichloro)phenyl]methyl}piperidin-4-amine L-Tartrate**

**Method 1**

- (i) To a stirred solution of 1-butoxycarbonyl-N-(3-methoxypropyl)piperidin-4-amine (0.50g, 1.84mmol) and 2,4-dichlorobenzaldehyde (0.64g, 3.67mmol) in dry tetrahydrofuran (10 ml) at room temperature was added sodium triacetoxymethylborohydride (0.97g, 4.60mmol). Aq. saturated sodium bicarbonate was added followed by dichloromethane (15 ml). After stirring for 5min, the organic phase was isolated using a phase separator and evaporated to give a crude oil. Purified on a 40g cartridge of silica using an ISCO combiflash by gradient elution with iso-hexane-ethyl acetate (10 to 40%) to give the required product 1-butoxycarbonyl-N-(3-methoxypropyl)-N-{[(2,4-dichloro)phenyl]methyl}piperidin-4-amine contaminated with 2,4-dichlorobenzyl alcohol as a colourless oil. Taken on to next step without further purification.
- (ii) A solution of 1-butoxycarbonyl-N-(3-methoxypropyl)-N-{[(2,4-dichloro)phenyl]methyl}piperidin-4-amine (0.76g) in dichloromethane (10 ml) was stirred at room temperature with trifluoroacetic acid (1.36 ml) overnight. The reaction mixture was evaporated and the resulting oil was dissolved in methanol and purified on SCX-2 column (5g) eluting with methanol and methanolic ammonia to give a colourless

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oil (385mg). The oil was dissolved in methanol and L-tartaric acid (174mg) added, warmed to give a clear solution then allowed to stand over a vapour of diethyl ether. The crystals were filtered, washed with diethyl ether and dried *in vacuo* at 60°C to give the title product as a colourless solid (508mg). LCMS 3.37min. [M+H] 331; <sup>1</sup>NMR (d<sup>6</sup>-

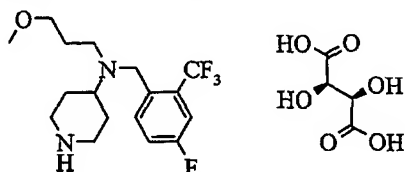
5 DMSO): 7.60 (2H, d), 7.44 (1H, d), 3.88 (2H, s), 3.67 (2H, s), 3.34-3.23 (4H, m), 3.17 (3H, s), 2.88-2.68 (3H, m), 2.57-2.50 (2H, m), 1.88-1.77 (2H, m), 1.76-1.50 (4H, m).

#### Method 2

(i) To a stirred solution of 1-butoxycarbonyl-N-(3-methoxypropyl)piperidin-4-amine (8.16g; 0.03 mol) and 2,4-dichlorobenzaldehyde (10.5g, 0.06 mol) in dry THF (120 ml) was added in one portion at room temperature sodium triacetoxymethylborohydride (15.9g; 0.075 mol). The reaction was stirred for 24h. Dichloromethane and saturated aqueous sodium bicarbonate were then added and the product extracted several times with dichloromethane. The organic extracts were collected and washed with brine, dried over anhydrous magnesium sulphate. After filtration the solvent was removed *in vacuo* to leave a clear oil (18g). This was purified in 2 batches using 2x120g silica cartridges on an ISCO combiflash via gradient elution with iso-hexane-ethyl acetate (10-40%) to yield after removal of solvent the product 1-butoxycarbonyl-N-(3-methoxypropyl)-N-[(2,4-dichloro)phenyl]methyl}piperidin-4-amine as a clear oil (9g).

(ii) A solution of 1-butoxycarbonyl-N-(3-methoxypropyl)-N-[(2,4-dichloro)phenyl]methyl}piperidin-4-amine (9g; 0.025mol) in dichloromethane (100ml) was stirred at room temperature with trifluoroacetic acid (16.5 ml) overnight under a nitrogen atmosphere. The solvent/TFA was removed *in vacuo* and the resulting oil dissolved in dichloromethane and aqueous sodium hydroxide added (2N; 30 ml). The product was extracted several times with dichloromethane and the combined extracts washed with water. After drying with magnesium sulphate and filtering, the solvent was removed to yield a clear oil (6.9g). The oil was dissolved in methanol (40 ml) and warmed to 50°C on a steam bath. L-tartaric acid (3.13g; 0.0208mol) was dissolved in methanol (15 ml) with heating and the solutions combined at 50°C. Diethyl ether (40 ml) was slowly added to the cooling solution. The crystals produced were filtered and washed with cold methanol-ether mixture and dried at 60°C *in vacuo* to give the title product as a colourless solid (7.16g).

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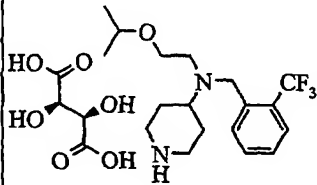
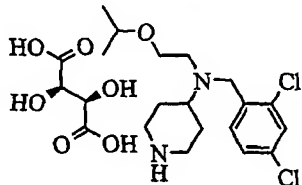
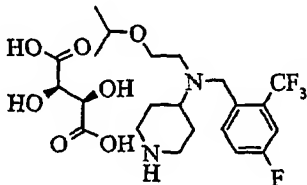
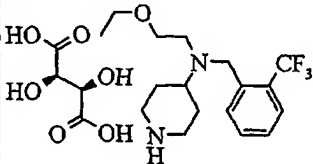
**EXAMPLE 182:****N-(3-Methoxypropyl)-N-{[(4-fluoro-2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine -L Tartrate**

- 5 (i) To a stirred solution of 1-butoxycarbonyl-N-(3-methoxypropyl)piperidin-4-amine (0.50g, 1.84mmol) and 4-fluoro-2-trifluoromethylbenzaldehyde (0.70g, 3.67mmol) in dry tetrahydrofuran (10 ml) at room temperature was added sodium triacetoxymethylborohydride (0.97g, 4.60mmol). Aq. saturated sodium bicarbonate was added followed by dichloromethane (15 ml). After stirring for 5min, the organic phase was isolated using a
- 10 phase separator and evaporated to give a crude oil. Purified on a 40g cartridge of silica using an ISCO combiflash by gradient elution with iso-hexane-ethyl acetate (10 to 40%) to give the required product 1-butoxycarbonyl-N-(3-methoxypropyl)-N-{[(4-fluoro-2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine contaminated with 4-fluoro-2-trifluoromethylbenzylalcohol as a colourless oil. Taken on to next step without further
- 15 purification.
- (ii) A solution of 1-butoxycarbonyl-N-(3-methoxypropyl)-N-{[(4-fluoro-2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine (0.18g) in dichloromethane (10ml) was stirred at room temperature with trifluoroacetic acid (0.31 ml) overnight. The reaction mixture was evaporated and the resulting oil was dissolved in methanol and
- 20 purified on SCX-2 column (5g) eluting with methanol and methanolic ammonia to give a colourless oil (95mg). The oil was dissolved in methanol and L-tartaric acid (40mg) added, warmed to give a clear solution then allowed to stand over a vapour of diethyl ether. The crystals were filtered, washed with diethyl ether and dried *in vacuo* at 60°C to give the title product as a colourless solid (106mg). LCMS Rt= 4.26min. [M+H]<sup>+</sup> 349.
- 25 <sup>1</sup>NMR (d<sup>6</sup>-DMSO): 7.90 (1H, t), 7.60-7.50 (2H, m), 3.88 (2H, s), 3.75 (2H, s), 3.34-3.23 (4H, m), 3.17 (3H, s), 2.88-2.70 (3H, m), 2.57-2.48 (2H, m), 1.88-1.77 (2H, m), 1.76-1.50 (4H, m).

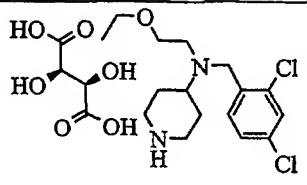
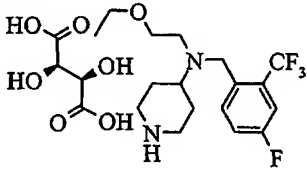
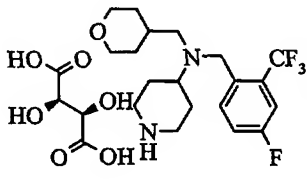
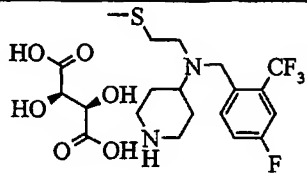
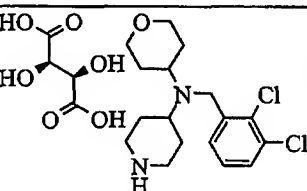
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Table 4 examples 183- 193 were similarly prepared.

**Table 4**

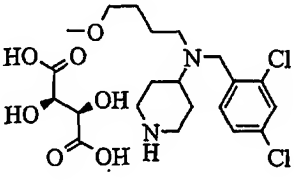
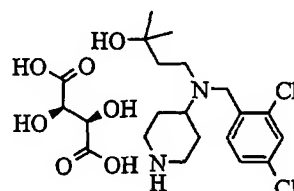
Example No.	Structure	Name	LCMS (12 min or 6 min*) $M^+ + 1$
183		N-{2-[(1-Methylethyl)oxy]ethyl}- N-[(2-(trifluoromethyl))phenyl]methyl}pip eridin-4-amine L-Tartrate	4.79 min, 345
184		N-{2-[(1-Methylethyl)oxy]ethyl}- N-[(2,4-dichloro)phenyl]methyl}piperidin-4- amine L-Tartrate	4.56 min, 345/347
185		N-{2-[(1-Methylethyl)oxy]ethyl}- N-[(4-fluoro-2-(trifluoromethyl))phenyl]methyl}pip eridin-4-amine L-Tartrate	5.24 min, 363
186		N-[2-(Ethyloxy)ethyl]-N-[(2-(trifluoromethyl))phenyl]methyl}pip eridin-4-amine L-Tartrate	4.47 min, 331

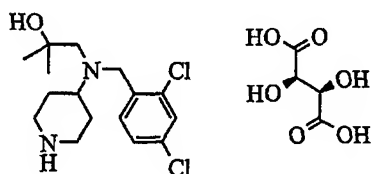
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187		N-[2-(Ethoxy)ethyl]-N-{[2,4-dichlorophenyl]methyl}piperidin-4-amine L-Tartrate	4.26 min, 331/333
188		N-[2-(Ethoxy)ethyl]-N-{[(4-fluoro-2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine L-Tartrate	4.90 min, 349
189		N-{[(4-Fluoro-2-trifluoromethyl)phenyl]methyl}-N-(tetrahydro-2H-pyran-4-ylmethyl)-piperidin-4-amine fumarate	2.18 min*, 375.2
190		N-[(2-(Methylthio)ethyl)-N-{[(4-fluoro-2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine L-Tartrate	5.19 min, 351
191		N-{[(2,3-Dichloro)phenyl]methyl}-N-tetrahydro-2H-pyran-4-yl-piperidin-4-amine L-Tartrate	4.63 min, 343.1/345.1



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192		N-{4-[(Methyl)oxy]butyl}-N-{[(2,4-dichloro)phenyl]methyl}piperidin-4-amine L-Tartrate	3.50 (M <sup>+</sup> +H) = 346
193		N-(3-hydroxy-3-methylbutyl)-N-{[(2,4-dichlorophenyl)methyl]piperidin-4-amine L-Tartrate	2.94 min, 346

**EXAMPLE 194:****N-(2-hydroxy-2-methylpropyl)-N-{[(2,4-dichlorophenyl)methyl]piperidin-4-amine L-Tartrate**

- 5 (i) To a stirred solution of isobutylene oxide (18.6g, 0.257mol) in acetonitrile (200 ml) cooled to 5°C was added lithium perchlorate (27.7g, 0.26mol) portionwise. The suspension was stirred at room temperature for 0.5h to give a solution. A solution of 1,1-dimethylethyl 4-({[2,4-dichlorophenyl]methyl} amino)piperidine-1-carboxylate (10.0g, 27.83mmol) in acetonitrile (200 ml) was then added dropwise over a period of
- 10 approximately 30min. The reaction mixture was heated at reflux for 24h, cooled and concentrated under vacuum. The concentrate was taken up in dichloromethane (200 ml) and washed with water (150 ml) and brine. The organic phase was dried over anhydrous magnesium sulphate, filtered and evaporated to a pale yellow oil. The crude oil was purified using a combiflash on a redisepp column (120g) by gradient elution with iso-
- 15 hexane-ethyl acetate (10-45%) over 35 min to give 1,1-dimethylethyl 4-({[2,4-

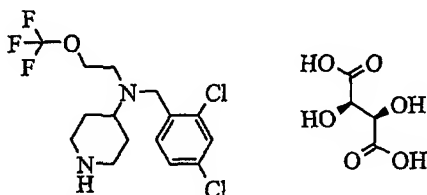
-162-

dichlorophenyl)methyl} {2-hydroxy-2-methylpropyl} amino)piperidine-1-carboxylate as a colourless oil (7.0g).

- (ii) To a stirred solution of 1,1-dimethylethyl 4-({[2,4-dichlorophenyl)methyl} {2-hydroxy-2-methylpropyl} amino)piperidine-1-carboxylate (7.0g, 16.24mmol) in dichloromethane (80 ml) at room temperature was added trifluoroacetic acid (18.5g, 0.16mol). The solution was stirred at room temperature for 17h, concentrated to approximately half volume and with ice cooling made basic with aqueous sodium hydroxide (2M). The organic phase was separated and the aqueous phase extracted twice with dichloromethane. The combined organic phases was washed twice with water and then with brine, dried over anhydrous magnesium sulphate, filtered and evaporated to a pale yellow oil. The oil was dissolved in warm methanol and a solution of L-tartaric acid (1eq) in methanol added. Diethyl ether was added and the resulting crystals filtered, washed with diethyl ether and dried under vacuum at 40-45°C to give the title compound as a colourless solid 4.85g. LCMS (12 min) Rt= 4.54min [M+H]<sup>+</sup> 331.3. <sup>1</sup>H NMR (400 MHz, MeOH-D<sub>4</sub>) 7.51 (1H, d), 7.23 (1H, s), 7.14 (1H, d), 4.14 (1H, s), 3.75 (2H, s), 3.29-3.18 (2H, m), 2.75-2.56 (3H, m), 2.38 (2H, s), 1.93-1.82 (2H, m), 1.68-1.50 (2H, m) 0.92 (6H, s).

#### **EXAMPLE 195:**

- N-{2-[(Trifluoromethyl)oxy]ethyl}-N-[(2,4-dichloro)phenyl)methyl]piperidin-4-amine L-Tartrate**



- (i) Tetrabutylammonium sulfate (10.2 ml, 8.78 mmol) was added to diethyleneglycol (15g, 141 mmol), followed by 50% aqueous NaOH solution (285 ml, ~12.5 M). The reaction was stirred for 10 minutes, and then carbon disulfide (285 ml) was added dropwise over 20 minutes, followed by MeI (43.7g, 308 mmol). The reaction was stirred at ambient temperature for 4 hours before water (50 ml) was added. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined

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organic extracts were washed with aqueous saturated sodium chloride, dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. The crude material was purified on silica gel eluting with 70% dichloromethane/hexanes to yield (18.80g, 47%) of dithiocarbonic acid *S*-methyl ester *O*-[2-(2-methylsulfanylthiocarboxyethoxy)-ethyl] ester:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 4.6 (4H, m), 3.8 (4H, m), 2.5 (6H, s).

(iia) HF-pyridine complex (42 ml) followed by dithiocarbonic acid *S*-methyl ester *O*-[2-(2-methylsulfanylthiocarboxyethoxy)-ethyl] ester (8.4g, 29.3mmol), was added to a cold ( $-78^\circ\text{C}$ ) solution of 1,3-dibromo-5,5-dimethylhydantoin (51.18g, 179 mmol) in dichloromethane (300 ml). The reaction was warmed to ambient temperature and stirred for 1.5 hours, then poured into cold aqueous saturated sodium chloride. The layers were separated, and the aqueous layer extracted with dichloromethane. The combined organic extracts were washed with cold 37% aqueous  $\text{NaHSO}_3$  and cold aqueous saturated sodium chloride then dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo* at ambient temperature. The residue was purified by bulb to bulb distillation under mild vacuum at  $120^\circ\text{C}$  and trapped at  $-78^\circ\text{C}$  to yield (5.81g, 82%) of 1-trifluoromethoxy-2-(2-trifluoromethoxyethoxy)-ethane:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 4.0 (4H, m), 3.70 (4H, m).

(iib) A tube was charged with 1-trifluoromethoxy-2-(2-trifluoromethoxyethoxy)-ethane (5.81g, 24mmol). Trifluoroacetic acid (0.55 ml, 6.2mmol) and trifluoroacetic anhydride (16 ml, 95.1mmol) were added, the tube sealed well under  $\text{N}_2$  atmosphere, and then immersed in a  $60^\circ\text{C}$  heated oil bath and heated for 5 days. The tube was removed from the oil bath and cooled to room temperature. The reaction mixture was concentrated *in vacuo* with ambient temperature bath. The residue was partitioned between dichloromethane and water, the layers were separated, the organic layer was dried over  $\text{MgSO}_4$ , and concentrated *in vacuo*. The crude material was purified by bulb to bulb distillation with mild vacuum at  $120^\circ\text{C}$  and trapped at  $-78^\circ\text{C}$  to yield (7.26g, 58%) of trifluoro-methanesulfonic acid 2-trifluoromethoxy-ethyl ester:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 4.69 (2H, m), 4.27 (2H, m).

(iic) Trifluoro-methanesulfonic acid 2-trifluoromethoxy-ethyl ester (0.541g, 2.06 mmol) was added to a solution of 4-(2,4-dichloro-benzylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (0.76g, 2.13 mmol) and  $\text{K}_2\text{CO}_3$  (0.626g, 4.53mmol) in anhydrous acetonitrile

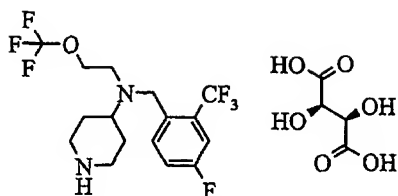
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- (5 ml). The reaction mixture was stirred at ambient temperature overnight then water and dichloromethane were added. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts was dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. The crude material was purified on silica gel eluting with 15% EtOAc/hexanes to yield (0.59g, 61%) 4-[(2,4-dichloromethyl-benzyl)-(2-trifluoromethoxy-ethyl)-amino]-piperidine-1-carboxylic acid *tert*-butyl ester:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.50 (1H, d), 7.35 (1H, d), 7.23 (1H, dd), 4.18 (2H, brs), 3.87-3.81 (2H, m), 3.78 (2H, s), 2.89-2.83 (2H, m), 2.67-2.56 (2H, m), 1.77 (2H, brd), 1.48-1.38 (12H, m).
- 10 (iii) 4-[(4-Fluoro-2-trifluoromethyl-benzyl)-(2-trifluoromethoxy-ethyl)-amino]-piperidine-1-carboxylic acid *tert*-butyl ester (0.59g, 1.26mmol) was added to a stirred solution of dichloromethane (30 ml) and anisole (0.684 ml, 6.29mmol). The reaction was cooled to  $0^\circ\text{C}$ . Trifluoroacetic acid (10 ml, 130mmol) was then added. The reaction was stirred for 30 minutes at  $0^\circ\text{C}$ . The reaction was loaded onto an SCX-2 (10g) column and washed with methanol (200 ml). The product was then eluted with 2M ammonia in methanol (100 ml) and concentrated to yield (0.413g, 88%) of (2,4-dichloro-benzyl)-piperidin-4-yl-(2-trifluoromethoxy-ethyl)-amine: mass spectrum (ion spray):  $m/z$  = 371 ( $M+1$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  = 7.60 (1H, d), 7.40 (1H, d), 7.29 (1H, dd), 3.92-3.88 (2H, m), 3.84 (2H, s), 3.10 (2H, brd), 2.93-2.89 (2H, m), 2.69-2.49 (3H, m), 1.83 (2H, brd), 1.57-1.45 (2H, m).
- 20 (iv) L-Tartaric acid (0.175g, 1.17mmol) was added to a solution of (2,4-dichloro-benzyl)-piperidin-4-yl-(2-trifluoromethoxy-ethyl)-amine (0.41g, 1.11mmol) in methanol (5 ml). The solution was sonicated for 30 minutes at ambient temperature and concentrated. Water (3 ml) was added to the residue, and the material was lyophilized to yield (0.56g, 97%) of the title compound (ion spray):  $m/z$  = 371 ( $M+1$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  = 7.59 (1H, d), 7.43 (1H, d), 7.31 (1H, dd), 4.41 (2H, s), 3.95-3.90 (2H, m), 3.88 (2H, s), 3.45 (2H, brd), 3.00-2.82 (5H, m), 2.05 (2H, brd), 1.85-1.72 (2H, m).

**EXAMPLE 196:**

- 30 N-{2-[ (Trifluoromethyl)oxy]ethyl}-N-[[ (4-fluoro-2-(trifluoromethyl))phenyl]methyl]piperidin-4-amine L-Tartrate

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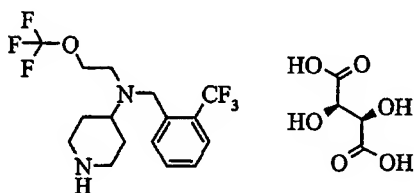


The title compound was prepared as example 195; mass spectrum (ion spray):  $m/z = 388$  (M);  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta = 7.95$  (1H, dd), 7.43 (1H, dd), 7.39-7.33 (1H, m), 4.44 (2H, s), 3.98-3.92 (4H, m), 3.45 (2H, brd), 3.00-2.81 (5H, m), 2.05 (2H, brd), 1.83-1.71 (2H, m).

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**EXAMPLE 197:**

**N-{2-[(Trifluoromethyl)oxy]ethyl}-N-[(2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine L-Tartrate**

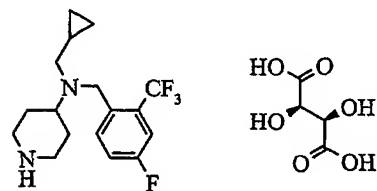


The title compound was prepared as example 195; mass spectrum (ion spray):  $m/z = 371$  (M+1);  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta = 7.92$  (1H, d), 7.66 (1H, d), 7.59 (1H, dd), 7.41 (1H, dd), 4.42 (2H, s), 4.00-3.92 (4H, m), 3.45 (2H, brd), 3.00-2.83 (5H, m), 2.05 (2H, brd), 1.85-1.72 (2H, m).

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**EXAMPLE 198:**

**N-(Cyclopropylmethyl)-N-[(4-fluoro-2-(trifluoromethyl))phenyl]methyl}piperidin-4-amine L-Tartrate**



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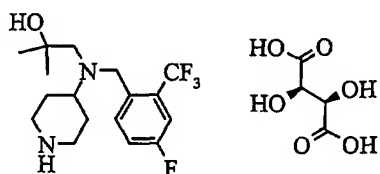
- (i) In a 1L Parr bottle, N-boc-4-piperidone (80g, 0.4mol) is dissolved in 0.4L THF. Under nitrogen stream, aminomethylcyclopropane (33g, 0.464mol, 1.16 equiv.) and 8g of 10% Pd/C are added and the resulting suspension is hydrogenated under 40 psi H<sub>2</sub> for 1 hour. The catalyst is filtered over Celite and the solution is evaporated to dryness to afford 106g (104%) of an oil which is used as it in the next step.
- (ii) In a 3-L double jacketed-reactor with overhead stirring (anchor-type), secondary amine (104g) is dissolved in THF (Roland - 1.0L ; 0.05%w/v water). Powdered NaHB(OAc)<sub>3</sub> (104.0g ; 1.2 equiv) and 2-trifluoromethyl-4-fluoro-benzaldehyde (66.7 mL ; 1.1 equiv) are added. Mass temperature rises from rt= 22.5°C to 27.3°C within 40min and then slowly decreases to rt= 22.5°C.). After 8h, powdered NaHB(OAc)<sub>3</sub> (21.5g ; 0.25 equiv) and 2-trifluoromethyl-4-fluoro-benzaldehyde (11.1 mL ; 0.2 equiv) are added. Mixture is allowed to stir overnight at rt= 22.5°C. After 23h, <sup>1</sup>H NMR ratio of starting material vs product is 1:5.4. NaHB(OAc)<sub>3</sub> (21.5g ; 0.25 equiv) and 2-trifluoromethyl-4-fluoro-benzaldehyde (11.1 mL ; 0.2 equiv) are added. One hour later, ratio is 1:5.8. Reaction is allowed to stir at rt=23°C for another 24h. <sup>1</sup>H NMR ratio of starting material vs product after a total of 48h is 1:20. Reaction is left under minimum stirring for the weekend. The mixture is cooled down to 0°C and water (400 mL) is added ( $\Delta T_m=12.5^\circ\text{C}$ ). Once  $\Delta T_m$  max is reached, T<sub>j</sub> is set to 20°C. Once T<sub>m</sub>=20°C, MTBE (800mL) is added. Layers are separated and aqueous layer, whose pH=5-6, is extracted by MTBE (400mL). Organic layers are pooled and washed with NaOH 2N (2x400mL), NaCl 10% (2x 400 mL) and evaporated to dryness to yield tertiary amine containing 2-trifluoromethyl-4-fluororbenzylic alcohol (221.7g - 82.2%area).
- (iii) In a 3-L double jacketed-reactor with overhead stirring (anchor-type), HCl 37% (Merck p.a. - 150 mL) is diluted in water (500 mL). The solution is heated up to 65°C. The neat tertiary amine (221.7g) is added dropwise. However, after 10% of the addition, we observed that the tertiary amine is immiscible in the aqueous system and that no reaction occurs (no gas evolution). THF (150 mL) is added to the reactor in order to solubilise the tertiary amine. The reaction starts instantaneously. Addition of the remaining 90% of tertiary amine is restarted and completed within 20min. After 30min post-stirring at 65°C, HPLC shows that the reaction is completed. The mixture is cooled

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- down to 20°C within 1h. Aqueous layer is washed with MTBE (3x400 mL). Tj is set to 10°C and the mixture is basified by NaOH 15%. Tm rises from 18°C to 28°C. Basic mixture (pH=14) is cooled to 23°C and extracted with MTBE (2x800mL). Organic layer is washed with NaCl 10% (400 mL) and then evaporated to dryness to yield (124g –
- 5 99.5%area). Yield from secondary amine: 92%.
- (iv) In a 3-L double jacketed-reactor with overhead stirring (anchor-type), amine (115.5g) is dissolved in i-PrOH. The solution is heated up to 70°C. Mixture is seeded with title product (1g) after each quarter of addition of a solution of L-tartaric acid (52.5g, 1.0equiv) in water (40 mL), until crystallisation occurs. It effectively occurs during
- 10 addition of the third quarter of L-tartaric acid solution. The remaining acid is added. The mixture is allowed to cool down to 20°C slowly (75min) and is then stirred at 20°C during 1h 30min. Suspension is filtered on fritted glass (P3), filtration is quick : 5min under 0.4 bar vacuum. Reactor is rinsed with mother liquors and the crystals are refiltered on the cake. Filtration is slower but no compression of the cake is noticed. The title
- 15 product is washed with i-PrOH (750 mL) and dried under vacuum at 40°C. Yield = (96% ,167.2g)

**EXAMPLE 199:**

20 **2-Methylpropan-2-ol-1-[[[(4-fluoro-2-(trifluoromethyl)phenyl)methyl]piperidin-4-amine] L-Tartrate**



- (i) Isobutylene oxide (2.5 mL, 27.74 mmol) was added to a solution of 4-(4-fluoro-2-trifluoromethyl-benzylamino)-piperidine-1-carboxylic acid tert-butyl ester (1.01g, 26.83 mmol) in anhydrous methanol (11mL). The reaction was stirred at ambient temperature for 3 days, then at reflux for 5h. The reaction mixture was cooled to ambient temperature and LiClO<sub>4</sub> (0.42g, 3.94 mmol) was added. The reaction was stirred at ambient
- 25 temperature overnight, then at reflux for 5 days. The cooled reaction was poured into 100mL of aqueous saturated NaHCO<sub>3</sub> and extracted with ethyl acetate (100 mL x3). The

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ethyl acetate was dried over sodium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel eluting with 30% EtOAc/hexanes to yield (0.85g, 71%) of 4-[(4-fluoro-2-trifluoromethyl-benzyl)-(2-hydroxy-2-methyl-propyl)-amino]-piperidine-1-carboxylic acid *tert*-butyl ester: mass spectrum (ion spray):

5  $m/z = 449$  (M+1);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.92\text{--}7.88$  (1H, m), 7.34 (1H, dd), 7.29-7.23 (1H, m), 4.16 (2H, brs), 3.99 (2H, s), 2.60-2.45 (6H, m), 1.76 (2H, brd), 1.48-1.37 (11H, m), 1.16 (6H, s).

(ii) 4-[(4-Fluoro-2-trifluoromethyl-benzyl)-(2-hydroxy-2-methyl-propyl)-amino]-piperidine-1-carboxylic acid *tert*-butyl ester (0.845g, 18.84 mmol) was added to a stirred  
10 solution of dichloromethane (5mL) and anisole (9.0mL, 82.8 mmol). The reaction was cooled to 0°C. Trifluoroacetic acid (6.0mL, 72.9 mmol) was then added. The reaction was stirred for 5 minutes at 0°C and then for 2h at room temperature. The reaction was loaded onto an SCX-2 (10g) column and washed with methanol (200mL). The product was then eluted with 2M ammonia in methanol (100mL) and concentrated to yield  
15 (0.603g, 92%) of 1-(4-fluoro-2-trifluoromethyl-benzyl)-piperidin-4-yl-amino]-2-methyl-propan-2-ol: mass spectrum (ion spray):  $m/z = 349$  (M+1);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.90$  (1H, dd), 7.33 (1H, dd), 7.28-7.22 (1H, m), 3.99 (2H, s), 3.11 (2H, brd), 2.58 (2H, s), 2.50-2.38 (3H, m), 1.78 (2H, brd), 1.51-1.39 (2H, m), 1.15 (6H, s).

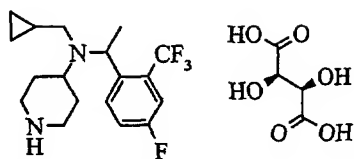
(v) L-Tartaric acid (0.25g, 1.66mmol) was added to a solution of 1-(4-fluoro-2-trifluoromethyl-benzyl)-piperidin-4-yl-amino]-2-methyl-propan-2-ol (0.58g, 1.66 mmol)  
20 in methanol (15mL). The solution was stirred for 1.5h at ambient temperature and concentrated. The solid was dried in a vacuum oven at 45°C overnight to yield (0.81g, 99%) 1-(4-fluoro-2-trifluoromethyl-benzyl)-piperidin-4-yl-amino]-2-methyl-propan-2-ol tartrate: mass spectrum (ion spray):  $m/z = 349$  (M+1);  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta = 8.17\text{--}8.10$  (1H, m), 7.44-7.34 (2H, m), 4.41 (2H, s), 4.03 (2H, s), 3.44 (2H, brd), 2.91-2.73 (3H, m), 2.55 (2H, s), 2.02 (2H, brd), 1.83-1.69 (2H, brd), 1.19 (6H, s).

#### EXAMPLE 200:

N-[1-(4-Fluoro-2-(trifluoromethyl)phenyl)ethyl]-N-(cyclopropylmethyl)piperidin-4-  
30 amine L-Tartrate



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- (i) To a solution of 4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (1.4 g, 7.03 mmol), cyclopropylmethylamine (500 mg, 7.03 mmol) and acetic acid (0.40 mL, 7.03 mmol) in 1,2-dichloroethane (69 mL) at 0 °C was added sodium triacetoxo-borohydride (2.08 g, 9.8 mmol). The reaction was warmed to ambient temperature and stirred for overnight under N<sub>2</sub>. The reaction mixture was poured on to 2N NaOH (50 mL) and extracted with ethyl acetate (3X). The combined organic extracts were washed with aqueous saturated NaCl, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The crude product was purified by flash chromatography on silica gel eluting with 5% EtOH (10% NH<sub>4</sub>OH)/chloroform to yield 1.32 g (74%) of 4-(Cyclopropylmethyl-amino)-piperidine-1-carboxylic acid *tert*-butyl ester: mass spectrum (ion spray): *m/z* = 255.1 (M+1); <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 4.11 (2H, m), 2.94-2.66 (3H, m), 2.52 (2H, d, *J*=7.0 Hz), 1.93 (2H, m), 1.50 (9H, s), 1.35-1.19 (2H, m), 1.05-0.91 (1H, m), 0.59-0.51 (2H, m), 0.24-0.18 (2H, m).
- (ii) Benzotriazole (326 mg, 2.75 mmol) and 4-(cyclopropylmethyl-amino)-piperidine-1-carboxylic acid *tert*-butyl ester (700 mg, 2.75 mmol) were dissolved in dry benzene (30 mL). 4-fluoro-2-trifluoromethyl benzaldehyde (0.38 mL, 2.75 mmol) was then added and the reaction was heated under reflux for overnight with a Dean-Stark trap. The reaction mixture was concentrated and the crude was dissolved in dry THF (20 mL). The reaction was cooled to 0°C and methylmagnesium bromide (3.0 M solution in Et<sub>2</sub>O, 1.1 mL, 3.02 mmol) was added dropwise. The reaction was stirred at ambient temperature for 1 hour. The reaction was quenched with saturated ammonium chloride and extracted with ethyl acetate (2X). The combined organic extracts were washed with aqueous saturated sodium chloride, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The crude product was purified by flash chromatography on silica gel eluting with 25% EtOAc /hexane to yield (174mg, 14%) of 4-{Cyclopropylmethyl-[1-(4-fluoro-2-trifluoromethyl-phenyl)-ethyl]-amino}-piperidine-1-carboxylic acid *tert*-butyl ester: mass spectrum (ion spray): *m/z* = 445.1 (M+1); <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ = 8.13-8.05 (1H, m), 7.43-7.36 (2H, m), 4.43-4.34 (1H, m), 4.17-4.03 (2H, m), 2.76-2.46 (4H, m), 2.27 (1H, dd, *J*=14.9, 7.0

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Hz), 1.81-1.71 (1H, m), 1.68-1.34 (16H, m), 0.88-0.77 (1H, m), 0.51-0.44 (2H, m), 0.13--0.04 (2H, m).

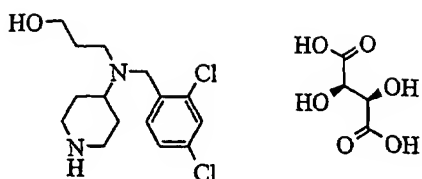
- (iii) 4-{Cyclopropylmethyl-[1-(4-fluoro-2-trifluoromethyl-phenyl)-ethyl]-amino}-piperidine-1-carboxylic acid *tert*-butyl ester (0.142 mg, 0.32 mmol) was added to a stirred solution of dichloromethane (1.5 mL) and anisole (2.5 mL, 23 mmol). Trifluoroacetic acid (1.0 mL, 12.15 mmol) was then added. The reaction was stirred for 2h at room temperature. The reaction was loaded onto an SCX-2 (10 g) column and washed with methanol (40 mL). The product was then eluted with 2M ammonia in methanol (25 mL) and concentrated to yield (0.104g, 95%) of cyclopropylmethyl-[1-(4-fluoro-2-trifluoromethyl-phenyl)-ethyl]-piperidin-4-yl-amine: mass spectrum (ion spray):  $m/z$  = 345.2(M+1);  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  = 8.13-8.06 (1H, m), 7.43-7.35 (2H, m), 4.42-4.32 (1H, m), 3.16-3.01 (2H, m), 2.75 (1H, dd,  $J$ =15.2, 7.3 Hz), 2.67-2.57 (1H, m), 2.49-2.39 (2H, m), 2.28 (1H, dd,  $J$ =15.2, 7.3 Hz), 1.86-1.77 (1H, m), 1.61-1.46 (3H, m), 1.39 (d, 3H,  $J$ =6.6 Hz), 0.90-0.78 (1H, m), 0.50-0.44 (2H, m), 0.15--0.04 (2H, m).
- (iv) L-Tartaric acid (39 mg, 0.26 mmol) was added to a solution of cyclopropylmethyl-[1-(4-fluoro-2-trifluoromethyl-phenyl)-ethyl]-piperidin-4-yl-amine (0.09 g, 0.26 mmol) in methanol (3 mL). The solution was stirred for 1.5h at ambient temperature and concentrated. The solid was dried in a vacuum oven at 45°C overnight to yield (0.125g, 97%) of the title product: mass spectrum (ion spray):  $m/z$  = 345.2 (M+1);  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  = 8.10-8.04 (1H, m), 7.45-7.38 (2H, m), 4.44-4.36 (3H, m), 3.50-3.36 (2H, m), 2.93-2.79 (3H, m), 2.75 (1H, dd,  $J$ =15.0, 5.3 Hz), 2.31 (1H, dd,  $J$ =15.0, 7.0 Hz), 2.06-1.97 (1H, m), 1.90-1.75 (3H, m), 1.41 (3H, d,  $J$ =6.6 Hz), 0.88-0.78 (1H, m), 0.52-0.45 (2H, m), 0.15--0.03 (2H, m).

HPLC Method: (100/0 to 5/95 0.2 % formic acid in water/0.2% formic acid in acetonitrile) Xterra MS C<sub>18</sub> 2.1mm x 50mm x 3.5micron, 6 minute run, 1.15 minutes retention time, 100% purity.

#### **EXAMPLE 201:**

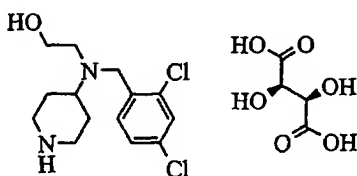
**N-(3-Hydroxypropyl)-N-[[[2,4-dichlorophenyl)methyl]](piperidin-4-amine L-Tartrate**

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(i) To 10% Pd/C (1.0 g, 10%wt), under nitrogen, was added a solution of the N-(tert-butoxycarbonyl)-4-piperidone (10g, 50mmol) and propanolamine (3.76g, 50mmol) in ethanol (50ml). This was hydrogenated for 1.5 hrs, at 65 psi hydrogen, using a PARR Hydrogenator. The catalyst was removed by filtration through Celite. Solvent was removed under vacuum to give the secondary amine as a colourless oil (12.8g, 100%) with >98% purity. LCMS (6 mins gradient):  $R_t = 1.93$  ( $M^+ + 1$ ) 259.4.

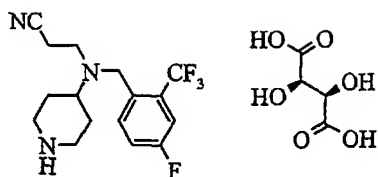
(ii) Prepared as example 177 to give the title compound. LCMS (12 min)  $R_t = 2.52$ ,  $M^+ + 1 = 317.1/319.1$ .  $^1\text{H NMR}$  (MeOD):  $\delta = 7.58$  (1H, d), 7.42 (1H, s), 7.33 (1H, d), 4.42 (2H, s), 3.80 (2H, s), 3.59-3.55 (2H, m), 3.46 (2H, brd), 3.32 (2H, s), 2.99-2.83 (3H, m), 2.73-2.68 (2H, m), 2.05-1.91 (2H, m), 1.90-1.87 (2H, m), 1.67-1.62 (2H, m).

**EXAMPLE 202:****N-(2-Hydroxyethyl)-N-[(2,4-Dichlorophenyl)methyl](piperidin-4-amine) L-****Tartrate**

This compound was prepared using the same method as for example 177 replacing 4-fluoro-2-(trifluoromethyl)benzaldehyde with 2,4-dichlorobenzaldehyde. LCMS- (12 mins gradient):  $R_t = 2.84$  ( $M^+ + 1$ ) 303.1/305.1;  $^1\text{H NMR}$  (MeOD):  $\delta = 7.51$  (1H, d), 7.30 (1H, s), 7.19 (1H, d), 4.29 (2H, s), 3.7 (2H, s), 3.41-3.30 (4H, m), 3.20 (1H, s), 2.90-2.70 (3H, m), 2.65-2.54 (2H, m), 1.95-1.88 (2H, brd), 1.75-1.60 (2H, m).

**EXAMPLE 203:****3-[(4-Fluoro-2-(trifluoromethyl)phenyl)methyl](piperidin-4-yl)amino]propanenitrile L-Tartrate**

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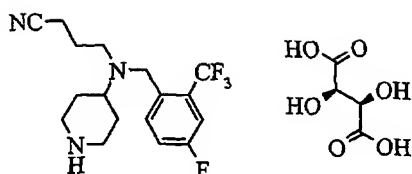


- (i) To a solution of N-(tert-butoxycarbonyl)-4-piperidone (1.0g, 5.0mmol, 1eq) and 3-aminopropionitrile (0.35g, 5.0mmol, 1eq) in THF (20ml) was added sodium triacetoxymethylborohydride (1.48g, 7.0mmol, 1.4eq) and the mixture stirred for 16 hours. The mixture was diluted with water (10 ml) and 2N sodium hydroxide (10 ml), and then
- 5 extracted with ethyl acetate (3 x 10 ml). The combined organic extracts were washed with brine (20 ml), dried (MgSO<sub>4</sub>) and the solvent removed *in vacuo* to give 1,1-dimethylethyl 4-[(2-cyanoethyl)amino]piperidine-1-carboxylate (0.88g, 70%) as a colourless oil. LCMS (6 min): Rt = 1.97 min, (M<sup>+</sup>+23) = 276.4.
- (ii) Prepared using a method similar to that described for example 180(ii) with 1,1-
- 10 dimethylethyl 4-[(2-cyanoethyl)amino]piperidine-1-carboxylate and 4-fluoro-2-(trifluoromethyl)benzaldehyde with additional purification using the Biotage Parallel Flex Purification System (UV-guided HPLC) followed by SCX-2 treatment prior to tartrate salt formation to give 3-[[[(4-fluoro-2-(trifluoromethyl)phenyl)methyl](piperidin-4-yl)amino]propanenitrile L-Tartrate (117mg, 38%) as a colourless solid. LCMS (12 min):
- 15 Rt = 4.53 min, (M<sup>+</sup>+1) = 330.1; <sup>1</sup>H NMR (300 MHz, MeOD): δ = 8.08-8.03 (1H, m, ArH), 7.47-7.38 (2H, m, ArH), 4.41 (2H, s, tartrate CH), 3.93 (2H, s, CH<sub>2</sub>Ar), 3.49-3.45 (2H, m, NCH<sub>2</sub>), 2.98-2.82 (5H, m, NCH), 2.58 (2H, t, J = 6.3, CHCN), 2.06 (2H, br. d, J = 13.6, CCH<sub>2</sub>) and 1.87-1.76 (2H, m, CCH<sub>2</sub>).

20 **EXAMPLE 204:**

**3-[[[(4-Fluoro-2-(trifluoromethyl)phenyl)methyl](piperidin-4-yl)amino]butanenitrile L-Tartrate**

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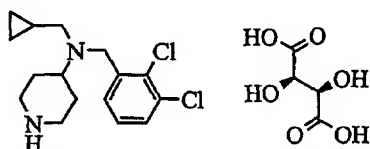


- (i) Prepared using a method similar to that described for example (203a) with 4-fluoro-2-(trifluoromethyl)benzylamine to give 1,1-dimethylethyl 4-((4-fluoro-2-(trifluoromethyl)phenyl)methyl)amino)piperidine-1-carboxylate (8.98g, 82%) as a colourless oil; LCMS (6 min):  $R_t = 3.00$  min,  $(M^+ + 1) = 377.1$ .
- 5 (ii) To a solution of 1,1-dimethylethyl 4-((4-fluoro-2-(trifluoromethyl)phenyl)methyl)amino)piperidine-1-carboxylate (0.49g, 1.3mmol, 1 eq) in acetonitrile (10 ml) was added potassium carbonate (0.37g, 2.6mmol 2 eq), sodium iodide (0.19g, 1.3mmol, 1 eq) followed by 4-bromobutyronitrile (1.5 ml, 15 mmol, 12eq). This was heated to reflux for 48hr, whereby reaction was incomplete so a further portion
- 10 of 4-bromobutyronitrile (0.37g, 2.6mmol, 12 eq) was added and heating to reflux was continued for 72 hrs. The reaction mixture was cooled, filtered and evaporated; the residue was diluted with methanol (5 ml) and loaded onto SCX-2 ion exchange cartridge (5g). The column was washed with methanol (15ml) and the product eluted with 2M ammonia in methanol solution (15 ml) then the solvent removed *in vacuo*. This oil was
- 15 purified by automated flash chromatography using an ISCO Combiflash system (40g  $\text{SiO}_2$ ) with a gradient of 0-40% ethyl acetate in *iso*-hexane over 40 minutes to give 1,1-dimethylethyl 4-((4-fluoro-2-(trifluoromethyl)phenyl)methyl)(3-cyanopropyl)amino)piperidine-1-carboxylate (220 mg, 38%) as a colourless oil. LCMS (6 min):  $R_t = 4.91$  min,  $(M^+ + 1) = 444.4$ .
- 20 (iii) To a solution of 1,1-dimethylethyl 4-((4-fluoro-2-(trifluoromethyl)phenyl)methyl)(3-cyanopropyl)amino)piperidine-1-carboxylate (220mg, 0.4mmol, 1 eq) in DCM (2 ml) was added trifluoroacetic acid (1 ml) and the mixture stirred at room temperature for 4 hours. The solvent was removed *in vacuo*, and then the residue was diluted with methanol (5 ml) and loaded onto SCX-2 ion exchange cartridge
- 25 (5g). The column was washed with methanol (15 ml), the product eluted with a solution of 2M ammonia in methanol (15 ml) and the solvent removed *in vacuo*. This was further purified on the Biotage Parallel Flex Purification System (UV-guided HPLC) followed by

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repeat SCX-2 treatment. The free base was taken up in hot methanol (1.0 ml) and added to L-tartaric acid (40mg, 1eq), diethyl ether was added slowly until crystallization occurred. After 16 hours the crystals were collected by filtration and dried in a vacuum oven at 40°C for 8 hours to give 3-[[4-Fluoro-2-

- 5 (trifluoromethyl)phenyl)methyl](piperidin-4-yl)amino]butanenitrile L-Tartrate (122 mg, 62%) as a colourless solid. LCMS (12 min):  $R_t = 4.40$  min,  $(M^+ + 1) = 344.1$   $^1\text{H}$  NMR (300 MHz, MeOD)  $\delta = 7.95\text{--}7.87$  (1H, m, ArH), 7.45–7.41 (2H, m, ArH), 4.41 (2H, s, tartrate CH), 3.86 (2H, s,  $\text{CH}_2\text{Ar}$ ), 3.49–3.45 (2H, m,  $\text{NCH}_2$ ), 3.00–2.81 (3H, m, NCH), 2.70 (2H, t,  $J = 6.5$ ,  $\text{NCH}_2$ ), 2.46 (2H, t,  $J = 6.8$ ,  $\text{CHCN}$ ), 2.08–2.04 (2H, m,  $\text{CCH}_2$ ) and  
10 1.84–1.73 (4H, m,  $\text{CCH}_2$ ), LCMS: 12 min,  $R_t = 4.40$  min,  $(M^+ + 1) = 344.1$

**EXAMPLE 205:****N-(Cyclopropylmethyl)-N-[[2,3-Dichloro)phenyl]methyl]piperidin-4-amine L-Tartrate**

- 15 (i) Prepared using a method similar to that described for example (179b) starting with 1,1-dimethylethyl 4-[[2,3-dichlorophenyl)methyl]amino}piperidine-1-carboxylate to give 1,1-dimethylethyl 4-[[2,3-dichlorophenyl)methyl](cyclopropylmethyl)amino}-piperidine-1-carboxylate (5.27g, 36%) as a yellow oil. LCMS: (6 min),  $R_t = 3.40$  min,  $(M^+ + 1) = 413.4$ .
- 20 (ii) To a solution of 1,1-dimethylethyl 4-[[2,3-dichlorophenyl)methyl](cyclopropylmethyl)amino}-piperidine-1-carboxylate (5.27g, 12.5mmol, 1eq) in DCM (20ml) was added trifluoroacetic acid (9.7 ml, 125mmol, 10 eq) and the mixture stirred at room temperature for 4 h. Water (50 ml) and *iso*-hexane (50 ml) were added and the aqueous layer separated. This was basified with 2N aqueous  
25 sodium hydroxide (60 ml) and extracted with a 1:1 mixture of diethyl ether and *iso*-hexane (3 x 50 ml). The combined organic extracts were dried ( $\text{MgSO}_4$ ) and the solvent removed *in vacuo*. This oil was purified by automated flash chromatography using an ISCO Combiflash system (120g  $\text{SiO}_2$ ) with a gradient of 0–40% of a 5% ammonia in

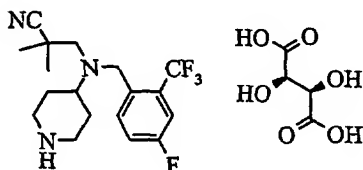
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methanol solution in DCM for 30 mins to give an oil. The product was taken up in hot methanol (26 ml) and added to L-tartaric acid (1.25mg, 1 eq), diethyl ether was added slowly until crystallization occurred. After 16 hours the crystals were collected by filtration and dried in a vacuum oven at 40°C for 16 hours to give N-

- 5 (Cyclopropylmethyl)-N-[(2,3-dichlorophenyl)methyl]piperidin-4-amine L-Tartrate (3.7 g, 64%) as a colourless solid. LCMS: (12 min): Rt = 3.17 min, (M<sup>+</sup>+1) = 313.1. <sup>1</sup>H NMR (300 MHz, MeOD): δ = 7.61-7.57 (1H, m, ArH), 7.35-7.32 (1H, m, ArH), 7.23-7.17 (1H, m, ArH), 4.32 (2H, s, tartrate CH), 3.83 (2H, s, CH<sub>2</sub>Ar), 3.40-3.36 (2H, m, NCH<sub>2</sub>), 3.02-2.85 (3H, m, NCH), 2.42 (2H, d, J = 6.6), 1.98 (2H, br d, J = 13.4), 1.79-1.67 (2H, m),  
10 0.82-0.69 (1H, m, CH), 0.40-0.34 (2H, m) and 0.03-0.00 (2H, m).

#### **EXAMPLE 206:**

#### **3-[(4-Fluoro-2-(trifluoromethyl)phenyl)methyl](piperidin-4-yl)amino]2,2-dimethylpropanenitrile L-Tartrate**



- 15 (i) To a solution of diisopropylamine (0.44 ml, 3.1mmol, 2.5eq) in THF (6 ml) at 0°C was added dropwise a solution of 1.6M n-butyllithium in hexanes (1.9 ml, 3.1mmol, 2.5eq). This was stirred at 0°C for 30 mins to form the lithium diisopropylamide. Half of the solution of this lithium diisopropylamide solution was added dropwise to a solution of 1,1-dimethylethyl 4-[(2-cyanoethyl)amino]piperidine-1-carboxylate (537mg, 1.25mmol,  
20 1eq) in THF (2 ml) at -78°C. After 30 min methyl iodide (0.08 ml, 1.25 mmol, 1eq) was added and the mixture was allowed to slowly warm to room temperature over 30 mins. The solution was then cooled back to -78°C and the second portion of lithium diisopropylamide was added dropwise followed by methyl iodide (0.08ml, 1.25mmol, 1eq) 30 mins later. This was again allowed to warm slowly to room temperature over 30  
25 mins then quenched with saturated aqueous ammonium chloride (20 ml). The aqueous layer was separated and extracted with ethyl acetate (3 x 20 ml), the combined organic layers were washed with brine, dried (MgSO<sub>4</sub>) and the solvent removed *in vacuo*. To

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give an oil which was purified by automated flash chromatography using an ISCO Combiflash system (40g SiO<sub>2</sub>) with a gradient of 0-30% ethyl acetate in *iso*-hexane over 40 minutes to give 1,1-dimethylethyl 4-({[4-fluoro-2-(trifluoromethyl)phenyl]methyl}(2-cyano-2-methylpropyl)amino)piperidine-1-carboxylate (183 mg, 32%) as a yellow oil.

5 LCMS: 6 min, Rt = 5.74 min, (M<sup>+</sup>+1) = 458.2.

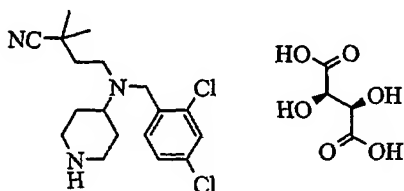
(ii) Prepared using a method similar to that described for example (204 c) with 1,1-dimethylethyl 4-({[4-fluoro-2-(trifluoromethyl)phenyl]methyl}(2-cyano-2-methylpropyl)amino)piperidine-1-carboxylate to give 3-[[[(4-Fluoro-2-(trifluoromethyl)phenyl)methyl](piperidin-4-yl)amino]2,2-dimethylpropanenitrile L-

10 Tartrate (42mg, 20%) as a colourless oil. LCMS: (12 min), Rt = 5.14 min, (M<sup>+</sup>+1) = 358.1. <sup>1</sup>H NMR (300 MHz, MeOD): δ = 8.05-7.96 (1H, m, ArH), 7.36-7.29 (2H, m, ArH), 4.29 (2H, s, tartrate CH), 4.00 (2H, s, CH<sub>2</sub>Ar), 3.38-3.34 (2H, m, NCH<sub>2</sub>), 2.83-2.62 (5H, m, NCH), 1.98 (2H, br. D, J = 13.7, CCH<sub>2</sub>), 1.75-1.67 (2H, m) and 1.23-1.22 (6H, m, 2 x CH<sub>3</sub>).

15

#### **EXAMPLE 207:**

#### **4-[[[(2,4-Dichlorophenyl)methyl](piperidin-4-yl)amino]-2,2-dimethylbutanenitrile L-Tartrate**



(i) To a solution of diisopropylamine (50.8 ml, 360mmol, 1.2eq) in THF (600 ml) at -78°C was added dropwise over 40 mins a solution of 1.6M n-butyllithium in hexanes (206 ml, 330mmol, 1.1eq), maintaining the temperature below -68°C. After stirring for 1 hr isobutyronitrile (27.2 ml, 300mmol, 1eq) was added dropwise over 20 minutes, maintaining the temperature below -70°C. The reaction was stirred for 2 hrs before addition of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) (54.4 ml, 450mmol, 1.5eq) in THF (40 ml) over 10 mins directly followed by bromoacetaldehyde diethyl acetal (45.2 ml, 300mmol, 1eq) over 10 minutes maintaining the temperature

20

25



- Methyl-phenyl-carbamic acid 4-tetrazol-1-ylmethyl-phenyl ester,  
 Methyl-phenyl-carbamic acid 4-(2,5-dioxo-pyrrolidin-1-ylmethyl)-phenyl ester, Methyl-phenyl-carbamic acid 4-[2-(2-thioxo-2H-pyridin-1-yl)-ethyl]-phenyl ester,  
 Methyl-phenyl-carbamic acid 4-(1,3-dioxo-1,3-dihydro-pyrrolo[3,4]pyridin-2-ylmethyl)-phenyl ester,  
 Methyl-phenyl-carbamic acid 4-[1,2,4]triazol-1-ylmethyl-phenyl ester,  
 Methyl-phenyl-carbamic acid 4-(2-thioxo-2H-pyridin-1-ylmethyl)-phenyl ester,  
 Methyl-phenyl-carbamic acid 4-[2-(1-methyl-1H-imidazol-2-ylsulfanyl)-ethyl]-phenyl ester,  
 Ethyl-phenyl-carbamic acid 4-(2-tetrazol-1-yl-ethyl)-phenyl ester,  
 Methyl-phenyl-carbamic acid 4-[2-(pyrimidin-2-yloxy)-ethyl]-phenyl ester,  
 Methyl-phenyl-carbamic acid 4-[2-(pyridin-4-ylsulfanyl)-ethyl]-phenyl ester,  
 Methyl-phenyl-carbamic acid 4-[2-(1-pyridin-3-yl-1H-imidazol-2-ylsulfanyl)-ethyl]-phenyl ester,  
 and  
 Methyl-phenyl-carbamic acid 4-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-phenyl ester.

15

Further examples of specific compounds of the invention are :

Benzyl-methyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester, and  
 Benzyl-methyl-carbamic acid 4-(3,5-dichloro pyridin-2-yloxy)-phenyl ester.

20

Further examples of specific compounds of the invention are :

- Isopropyl-methyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
 Cyclohexyl-methyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester.  
 Dimethyl-carbamic acid 4-(3,5-dichloro pyridin-2-yloxy)-phenyl ester,  
 Methyl-pyridin-2-yl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
 (2-Dimethylamino-ethyl)methylcarbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
 (6-Methoxy-pyridin-2-yl)-methyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
 (4-Methoxy-phenyl)-methyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
 (2-Methoxy-phenyl)-methyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
 (2-Carbamoyl-4-chloro-phenyl)-methyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
 (2-Carbamoyl-phenyl)-methyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
 (2-Chloro-phenyl)-methyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,

35

(2,4-Difluoro-phenyl)-methyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
and  
Methyl-(2-trifluoromethoxy-phenyl)-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl  
ester.

5

Further examples of specific compounds of the invention are :

Pyrrolidine-1-carboxylic acid 4-(3,5-dichloro-pyridin-2-yloxy)-phenyl ester,  
2,3-Dihydro-indole-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester. and  
1,3-Dihydro-isoindole-2-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester.

10

Further examples of specific compounds of the invention are :

Piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
Piperidine-1-carboxylic acid 3-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
Piperidine-1-carboxylic acid 4-(3,5-dichloro-pyridin-2-yloxy)-phenyl ester,  
15 Piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-ylamino)-phenyl ester,  
Piperidine-1-carboxylic acid 4-(3,5-dichloro-pyridin-4-yloxy)-phenyl ester,  
Piperidine-1-carboxylic acid 4-(4-trifluoromethyl-phenoxy)-phenyl ester,  
Piperidine-1-carboxylic acid 4-(2-cyano-5-trifluoromethyl-pyridine-3-yloxy)-phenyl ester,  
Piperidine-1-carboxylic acid 2-benzenesulfonyl-4-(3-chloro-5-trifluoromethyl-pyridine-2-  
20 yloxy)-phenyl ester,

Piperidine-1-carboxylic acid 4-tert-butoxy-phenyl ester,  
Piperidine-1-carboxylic acid 3-(4-fluorobenzyl)-4-methyl-2-oxo-2H-chromen-7-yl ester,  
Piperidine-1-carboxylic acid 4-phenoxy-phenyl ester,  
Piperidine-1-carboxylic acid 4-(4-chlorobenzoyl)-phenyl ester,  
25 Piperidine-1-carboxylic acid 4-(3-chloro-5-trifluoromethyl)-pyridine-2-yloxy)-phenyl ester,  
Piperidine-1-carboxylic acid 4-[4-(4-chloro-phenyl)-thiazol-2-yl]-phenyl ester,  
Piperidine-1-carboxylic acid 4-pyrrol-1-yl-phenyl ester,  
Piperidine-1-carboxylic acid 4-imidazol-1-yl-phenyl ester,  
Piperidine-1-carboxylic acid 4-(3-chloro-5-trifluoromethyl)-pyridine-2-ylmethyl)-phenyl ester,  
30 Piperidine-1-carboxylic acid 4-trifluoromethylsulfanyl-phenyl ester,  
Piperidine-1-carboxylic acid 4-pentafluoromethoxy-phenyl ester,  
Piperidine-1-carboxylic acid 4-benzyloxy-phenyl ester,  
Piperidine-1-carboxylic acid 4-benzyl-phenyl ester,  
Piperidine-1-carboxylic acid 4'-cyano-biphenyl-4-yl-ester,  
35 Piperidine-1-carboxylic acid 4'-bromo-biphenyl-4-yl-ester,

- Piperidine-1-carboxylic acid biphenyl-4-yl-ester,  
Piperidine-1-carboxylic acid 4-[3-(4-chlorophenyl)-ureido]-phenyl ester,  
Piperidine-1-carboxylic acid 4-(4-nitro-phenoxy)-phenyl ester,  
Piperidine-1-carboxylic acid 4-heptylsulfanyl-phenyl ester,  
5 Piperidine-1-carboxylic acid 4-butoxy-phenyl ester,  
Piperidine-1-carboxylic acid 4-(4-chloro-benzenesulfonyl)-phenyl ester,  
Piperidine-1-carboxylic acid 4-(4-chloromethyl-thiazol-2-yl)-phenyl ester,  
Piperidine-1-carboxylic acid 4-(4,4-dimethyl-2,6-dioxo-piperidin-1-yl)-phenyl ester,  
cis-Piperidine-1-carboxylic acid 4-(1,3-dioxo-octahydro-isoindol-2-yl)-phenyl ester,  
10 Piperidine-1-carboxylic acid 4-(cyclohexanecarbonyl-amino)-phenyl ester,  
Piperidine-1-carboxylic acid 4-(2-cyclohexyl-acetyl-amino)-phenyl ester,  
cis/trans-Piperidine-1-carboxylic acid 4-[(4-tert-butyl-cyclohexanecarbonyl)-amino]-phenyl ester,  
cis- Piperidine-1-carboxylic acid 4-[(4-tert-butyl-cyclohexanecarbonyl)-amino]-phenyl ester,  
15 trans- Piperidine-1-carboxylic acid 4-[(4-tert-butyl-cyclohexanecarbonyl)-amino]-phenyl ester,  
Piperidine-1-carboxylic acid 4-(3,3-dimethyl-butyrylamino)-phenyl ester,  
Piperidine-1-carboxylic acid 3-benzyl-4-methyl-2-oxo-2H-chromen-7-yl ester,  
Piperidine-1-carboxylic acid 3-(3,4-dichloro-benzyl)-4-methyl-2-oxo-2H-chromen-7-yl ester,  
Piperidine-1-carboxylic acid 3-(2-chloro-6-fluoro-benzyl)-4-methyl-2-oxo-2H-chromen-7-yl  
20 ester,  
Piperidine-1-carboxylic acid 3-(2,6-dichloro-benzyl)-4-methyl-2-oxo-2H-chromen-7-yl ester,  
Piperidine-1-carboxylic acid 3-(2,6-dichloro-benzyl)-6-chloro-4-methyl-2-oxo-2H-chromen-7-yl ester,  
Piperidine-1-carboxylic acid 6-chloro-3-(2-chloro-6-fluoro-benzyl)-4-n-propyl-2-oxo-2H-  
25 chromen-7-yl ester,  
Piperidine-1-carboxylic acid 3-(4-methoxy-phenyl)-4-methyl-2-oxo-2H-chromen-7-yl ester,  
Piperidine-1-carboxylic acid 4-methyl-2-oxo-3-phenyl-2H-chromen-7-yl ester,  
Piperidine-1-carboxylic acid 3-(2,5-dimethoxy-phenyl)-4-methyl-2-oxo-2H-chromen-7-yl ester,  
Piperidine-1-carboxylic acid 3-(3,4-dimethoxy-phenyl)-4-methyl-2-oxo-2H-chromen-7-yl ester,  
30 Piperidine-1-carboxylic acid 4-pyrrolidine-1-yl-phenyl ester,  
Piperidine-1-carboxylic acid 4-piperidine-1-yl-phenyl ester,  
Piperidine-1-carboxylic acid 4-morpholine-1-yl-phenyl ester,  
Piperidine-1-carboxylic acid 4-[(6-chloro-pyridine-3-carbonyl)-amino]-phenyl ester,  
Piperidine-1-carboxylic acid 4-[(6-chloro-pyridine-3-carbonyl)-amino]-phenyl ester,  
35 Piperidine-1-carboxylic acid 4-[(pyridine-2-carbonyl)-amino]-phenyl ester,

- Piperidine-1-carboxylic acid pyrazol-1-yl ester,  
Piperidine-1-carboxylic acid 3-bromo-pyrazol-1-yl ester,  
Piperidine-1-carboxylic acid 4-bromo-pyrazol-1-yl ester,  
Piperidine-1-carboxylic acid 5-bromo-pyrazol-1-yl ester,  
5 Piperidine-1-carboxylic acid 3,4,5-tribromo-pyrazol-1-yl ester,  
Piperidine-1-carboxylic acid 4-chloro-pyrazol-1-yl ester,  
Piperidine-1-carboxylic acid 4-iodo-pyrazol-1-yl ester,  
Piperidine-1-carboxylic acid 3-(4-methoxy-phenyl)-pyrazol-1-yl ester,  
Piperidine-1-carboxylic acid 3-(2-methoxy-phenyl)-pyrazol-1-yl ester,  
10 Piperidine-1-carboxylic acid 3-(4-nitro-phenyl)-pyrazol-1-yl ester,  
Piperidine-1-carboxylic acid 3-(2-fluoro-phenyl)-pyrazol-1-yl ester,  
Piperidine-1-carboxylic acid 3-pyridin-2-yl-pyrazol-1-yl ester,  
Piperidine-1-carboxylic acid 4-phenylsulfanyl-pyrazol-1-yl ester,  
Piperidine-1-carboxylic acid 3-thiophen-2-yl-pyrazol-1-yl ester,  
15 Piperidine-1-carboxylic acid 5-thiophen-2-yl-pyrazol-1-yl ester,  
Piperidine-1-carboxylic acid imidazol-1-yl ester,  
Piperidine-1-carboxylic acid 2-chloro-imidazol-1-yl ester,  
Piperidine-1-carboxylic acid 2-bromo-imidazol-1-yl ester,  
Piperidine-1-carboxylic acid 2-iodo-imidazol-1-yl ester,  
20 Piperidine-1-carboxylic acid 2-methyl-imidazol-1-yl ester,  
Piperidine-1-carboxylic acid 2-phenylsulfanyl-imidazol-1-yl ester,  
Piperidine-1-carboxylic acid 2-(4-methoxy-phenyl)-imidazol-1-yl ester,  
Piperidine-1-carboxylic acid 2-(4-fluoro-phenyl)-imidazol-1-yl ester,  
Piperidine-1-carboxylic acid 2-thiophen-2-yl-imidazol-1-yl ester,  
25 Piperidine-1-carboxylic acid 2-pyridin-2-yl-imidazol-1-yl ester,  
Piperidine-1-carboxylic acid 2,5-dichloro-imidazol-1-yl ester,  
Piperidine-1-carboxylic acid 4-bromo-2,5-dichloro-imidazol-1-yl ester,  
2-Methyl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
3-Methyl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
30 4-Methyl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
4-Benzyl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
1,4-Dioxo-8-aza-spiro[4.5]decane-8-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
3-Hydroxy-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
35 3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl es-

ter,

3,4-Dihydro-2H-quinoline-1-carboxylic acid 4-(3,5-dichloro-pyridin-2-yloxy)-phenyl ester,

3,4-Dihydro-2H-quinoline-1-carboxylic acid 4-(2-cyano-5-trifluoromethyl-pyridin-3-yloxy)-phenyl ester,

5 3,4-Dihydro-2H-quinoline-1-carboxylic acid 3-(3,4-dichloro-benzyl)-4-methyl-2-oxo-2H-chromen-7-yl ester,

3,4-Dihydro-2H-quinoline-1-carboxylic acid 3-benzyl-4-methyl-2-oxo-2H-chromen-7-yl ester,

3,4-Dihydro-2H-quinoline-1-carboxylic acid 3-(2-chloro-6-fluoro-benzyl)-4-methyl-2-oxo-2H-chromen-7-yl ester,

10 3,4-Dihydro-2H-quinoline-1-carboxylic acid 3-(2,6-dichloro-benzyl)-4-methyl-2-oxo-2H-chromen-7-yl ester,

3,4-Dihydro-2H-quinoline-1-carboxylic acid 3-(2,6-dichloro-benzyl)-6-chloro-4-methyl-2-oxo-2H-chromen-7-yl ester,

3,4-Dihydro-2H-quinoline-1-carboxylic acid 3-(4-fluoro-benzyl)-4-methyl-2-oxo-2H-chromen-15 7-yl ester,

3,4-Dihydro-2H-quinoline-1-carboxylic acid 6-chloro-3-(2-chloro-6-fluoro-benzyl)-4-n-propyl-2-oxo-2H-chromen-7-yl ester,

3,4-Dihydro-2H-quinoline-1-carboxylic acid 3-(4-methoxy-phenyl)-4-methyl-2-oxo-2H-chromen-7-yl ester,

20 3,4-Dihydro-2H-quinoline-1-carboxylic acid 4-methyl-2-oxo-3-phenyl-2H-chromen-7-yl ester,

3,4-Dihydro-2H-quinoline-1-carboxylic acid 3-(2,5-dimethoxy-phenyl)-4-methyl-2-oxo-2H-chromen-7-yl ester,

3,4-Dihydro-2H-quinoline-1-carboxylic acid 3-(3,4-dimethoxy-phenyl)-4-methyl-2-oxo-2H-chromen-7-yl ester,

25 7-Trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,

4-Hydroxymethyl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,

4-Oxo-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,

30 4-[5-(4-Dimethylamino-phenyl)-1H-pyrazol-3-yl]-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,

4-(5-Furan-2-yl-1H-pyrazol-3-yl)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,

4-Benzylamino-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,

35 4-(3,4-Dihydro-1H-isoquinolin-2-ylmethyl)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-

- pyridin-2-yloxy)-phenyl ester,  
3-Hydroxymethyl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
3-Hydroxy-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
5 4-Benzyl-4-hydroxy-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
4-Hydroxy-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
4-Pyrrolidin-1-yl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
10 4-Hydroxymethyl-piperidine-1-carboxylic acid 4-(5-chloro-pyridin-2-yloxy)-phenyl ester,  
1,4-Dioxo-8-aza-spiro[4.5]decane-8-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
4-Benzoyl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
[1,4']Bipiperidinyl-1'-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
15 4-(2-Oxo-2,3-dihydro-benzimidazol-1-yl)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
3-Diethylcarbamoyl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
4-Carbamoyl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
20 3-Carbamoyl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
4-(tert-Butyl-dimethyl-silanyloxy)-piperidine-1-carboxylic acid 5-benzoylamino-pyridin-2-yl ester,  
4-Hydroxy-piperidine-1-carboxylic acid 5-benzoylamino-pyridin-2-yl ester,  
4-Hydroxy-piperidine-1-carboxylic acid 5-trifluoromethyl-pyridin-2-yl ester,  
25 4-Hydroxy-piperidine-1-carboxylic acid 5-(4-chloro-benzoylamino)-pyridin-2-yl ester,  
4-Hydroxy-piperidine-1-carboxylic acid 5-(3-methoxy-benzoylamino)-pyridin-2-yl ester,  
4-Hydroxy-piperidine-1-carboxylic acid 5-(4-methoxy-benzoylamino)-pyridin-2-yl ester,  
4-Hydroxy-piperidine-1-carboxylic acid 5-(2,4-dichloro-benzoylamino)-pyridin-2-yl ester,  
4-Hydroxy-piperidine-1-carboxylic acid 5-(4-trifluoromethyl-benzoylamino)-pyridin-2-yl ester,  
30 4-Hydroxy-piperidine-1-carboxylic acid 4,4-dimethyl-2,6-dioxo-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-6'-yl ester,  
4-Hydroxy-piperidine-1-carboxylic acid 5-(5-trifluoromethyl-pyridin-2-yloxy)-pyridin-2-yl ester,  
4-Hydroxy-piperidine-1-carboxylic acid 5-(3,5-dichloro-pyridin-2-yloxy)-pyridin-2-yl ester,  
4-Aminomethyl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
35 4-Benzimidazol-1-yl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl

- ester,  
4-Hydroxymethyl-piperidine-1-carboxylic acid 4-(2-cyclohexyl-acetylamino)-phenyl ester,  
4-(4-Amino-phenyl)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl  
ester,  
5 4-(Methyl-pyridin-3-ylmethyl-amino)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-  
2-yloxy)-phenyl ester,  
4-(2-Oxo-pyrrolidin-1-yl)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-  
phenyl ester,  
4-(Methyl-phenethyl-amino)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-  
10 phenyl ester,  
4-[(Benzyl-ethyl-amino)-methyl]-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-  
yloxy)-phenyl ester,  
4-[Methyl-phenethyl-amino)-methyl]-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-  
2-yloxy)-phenyl ester,  
15 4-[(Cyclohexyl-methyl-amino)-methyl]-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-  
pyridin-2-yloxy)-phenyl ester,  
4-[(Ethyl-pyridin-4-ylmethyl-amino)-methyl]-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-  
pyridin-2-yloxy)-phenyl ester,  
4-[(Benzyl-methyl-amino)-methyl]-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-  
20 yloxy)-phenyl ester,  
4-[(Methyl-pyridin-3-ylmethyl-amino)-methyl]-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-  
pyridin-2-yloxy)-phenyl ester,  
4-(1,3-Dihydro-isoindol-2-ylmethyl)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-  
yloxy)-phenyl ester,  
25 4-Benzotriazol-1-yl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl  
ester,  
4-[(Cyclopropylmethyl-amino)-methyl]-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-  
2-yloxy)-phenyl ester,  
4-[Methyl-(2-pyridin-2-yl-ethyl)-amino]-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-  
30 pyridin-2-yloxy)-phenyl ester,  
4-(Cyclohexyl-methyl-amino)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-  
yloxy)-phenyl ester,  
4-(Isopropyl-methyl-amino)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-  
phenyl ester,  
35 4-Hydroxymethyl-piperidine-1-carboxylic acid 4-(3,3-dimethyl-butylcarbonyl)-phenyl ester

- ester,
- Piperidine-1-carboxylic acid 4,4-dimethyl-2,6-dioxo-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-6'-yl,  
4-[Methyl-(2-pyridin-4-yl-ethyl)-amino]-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-  
pyridin-2-yloxy)-phenyl ester,
- 5 4-(Cyclopropyl-pyridin-4-ylmethyl-amino)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-  
pyridin-2-yloxy)-phenyl ester,  
4-[Cyclopropyl-(2-fluoro-benzyl)-amino]-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-  
pyridin-2-yloxy)-phenyl ester,
- 10 4-(Cyclopropyl-pyridin-3-ylmethyl-amino)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-  
pyridin-2-yloxy)-phenyl ester,  
4-(Cyclopropylmethyl-pyridin-3-ylmethyl-amino)-piperidine-1-carboxylic acid 4-(5-  
trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
4-(Cyclopropylmethyl-pyridin-3-ylmethyl-amino)-piperidine-1-carboxylic acid 4-(5-  
trifluoromethyl-pyridin-2-yloxy)-phenyl ester,
- 15 4-(4-Hydroxy-piperidin-1-ylmethyl)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-  
yloxy)-phenyl ester,  
4-[3-[1-(2-Hydroxy-ethyl)-piperidin-4-yl]-propyl]-piperidine-1-carboxylic acid 4-(5-  
trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
4-(2-Pyrrolidin-1-yl-ethyl)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-  
phenyl ester,
- 20 4-Hydroxy-piperidine-1-carboxylic acid 4-[2-(toluene-4-sulfonylamino)-ethyl]-phenyl ester,  
4-Hydroxy-piperidine-1-carboxylic acid 4-[2-(5-pyridin-2-yl-thiophene-2-sulfonylamino)-ethyl]-  
phenyl,  
4-Hydroxy-piperidine-1-carboxylic acid 4-(5-pyridin-2-yl-thiophene-2-sulfonylamino)-phenyl  
ester,
- 25 4-Hydroxy-piperidine-1-carboxylic acid 4-pyridin-2-ylmethyl-phenyl ester,  
4-Hydroxy-piperidine-1-carboxylic acid 4-pyridin-3-ylmethyl-phenyl ester,  
4-Hydroxy-piperidine-1-carboxylic acid 4-(4-trifluoromethyl-benzyl)-phenyl ester,  
4-Hydroxy-piperidine-1-carboxylic acid 4-(5-methyl-pyridin-2-ylmethyl)-phenyl ester,
- 30 4-(3-Amino-phenyl)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl es-  
ter, 4-Phenyl-piperidine-1-carboxylic acid 4-(5-methyl-pyridin-2-ylmethyl)-phenyl ester, and  
4-(4-Methoxy-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid 4-(5-methyl-pyridin-2-  
ylmethyl)-phenyl ester.
- 35 Further examples of specific compounds of the invention are :



- 4-Methyl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
4-Benzyl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
4-(2-Hydroxyethyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl  
ester,
- 5 4-(Pyridin-2-yl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
4-(Pyrrolidinocarbonylmethyl)- piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-  
yloxy)-phenyl ester,  
4-Phenyl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
4-(Isopropylaminocarbonylmethyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-  
10 yloxy)-phenyl ester,  
4-Ethyl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
4-Propyl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
4-Butyl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
4-(4-Chlorobenzyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl  
15 ester,  
4-(4-Chlorophenyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl  
ester,  
4-(Diphenylmethyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl  
ester,
- 20 4-(3-Hydroxypropyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl  
ester,
- 4-(3-Trifluoromethylphenyl)- piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-  
phenyl ester,
- 25 4-(3-Chlorophenyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl  
ester,  
4-(2-Chlorophenyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl  
ester,  
4-(3,4-Dichlorophenyl)- piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-  
30 phenyl ester,  
4-(4-Fluorophenyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl  
ester,  
4-(4-Methoxyphenyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl  
ester,
- 35 4-(3-Methoxyphenyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl

- ester,  
4-(2-Methoxyphenyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl  
ester,  
4-(2,4-Dimethoxyphenyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-  
5 phenyl ester,  
4-(3,4,5-Trimethoxyphenyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-  
phenyl ester,  
4-[3-(Trifluoromethyl)pyridin-2-yl]-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-  
yloxy)-phenyl ester,  
10 4-(3,4-Methylenedioxy-phenyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-  
yloxy)-phenyl ester,  
4-(3,4-Methylenedioxy-benzyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-  
yloxy)-phenyl ester,  
4-(Pyridin-4-yl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
15 4-Cyclopentyl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
4-(2-Pyrimidinyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl es-  
ter,  
4-(4-Acetylphenyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl  
ester,  
20 4-(2-(2-Hydroxyethoxy)ethyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-  
yloxy)-phenyl ester,  
4-Benzyl-piperazine-1-carboxylic acid pyrazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid 3-bromo-pyrazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid 4-bromo-pyrazol-1-yl ester,  
25 4-Benzyl-piperazine-1-carboxylic acid 5-bromo-pyrazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid 3,4,5-tribromo-pyrazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid 4-chloro-pyrazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid 4-iodo-pyrazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid 3-(4-methoxy-phenyl)-pyrazol-1-yl ester,  
30 4-Benzyl-piperazine-1-carboxylic acid 3-(2-methoxy-phenyl)-pyrazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid 3-(4-nitro-phenyl)-pyrazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid 3-(2-fluoro-phenyl)-pyrazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid 3-pyridin-2-yl-pyrazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid 4-phenylsulfanyl-pyrazol-1-yl ester,  
35 4-Benzyl-piperazine-1-carboxylic acid 3-thiophen-2-yl-pyrazol-1-yl ester,

- 4-Benzyl-piperazine-1-carboxylic acid 5-thiophen-2-yl-pyrazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid imidazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid 2-chloro-imidazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid 2-bromo-imidazol-1-yl ester,  
5 4-Benzyl-piperazine-1-carboxylic acid 2-iodo-imidazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid 2-methyl-imidazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid 2-phenylsulfanyl-imidazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid 2-(4-methoxy-phenyl)-imidazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid 2-(4-fluoro-phenyl)-imidazol-1-yl ester,  
10 4-Benzyl-piperazine-1-carboxylic acid 2-thiophen-2-yl-imidazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid 2-pyridin-2-yl-imidazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid 2,5-dichloro-imidazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid 4-bromo-2,5-dichloro-imidazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid 4-bromo-2-chloro-imidazol-1-yl ester,  
15 4-Benzyl-piperazine-1-carboxylic acid 5-(4-methoxy-phenyl)-imidazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid 5-(4-fluoro-phenyl)-imidazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid 5-thiophen-2-yl-imidazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid 5-pyridin-2-yl-imidazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid 4-(5-chloro-pyridin-2-yloxy)-phenyl ester,  
20 4-Pyridin-3-ylmethyl-piperazine-1-carboxylic acid 4-(5-chloro-pyridin-2-yloxy)-phenyl ester,  
4-Pyridin-2-yl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)phenyl ester,
- 4-(1,3-Benzodioxol-5-yl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-  
25 phenyl ester,  
4-[2-(2-Hydroxyethoxy)ethyl]-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-  
yloxy)-phenyl ester,  
4-(Diphenylmethyl)piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl  
ester,  
30 4-(4-tert-Butylbenzyl)piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)phenyl  
ester,  
4-(4-Fluorobenzyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl  
ester,  
4-(2-Thienylethyl)piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)phenyl es-  
35 ter,

- 4-(1-Phenylethyl)piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)phenyl ester,  
4-Octylpiperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)phenyl ester,  
4-(3-Dimethylamino-propyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-  
5 phenyl ester,  
4-Pyrimidin-2-yl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
4-Cyclopropylmethyl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
10 4-Phenethyl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
4-Pyridin-2-ylmethyl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
4-Pyridin-3-ylmethyl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
15 4-(3-Phenylpropyl)piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
4-(4-Phenylbutyl)piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
4-(3,4-Dichlorophenyl)piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)phenyl  
20 ester,  
4-(4-Fluorophenyl)piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)phenyl ester,  
4-(2-Chlorophenyl)piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)phenyl ester,  
25 4-Methylpiperazine-1-carboxylic acid 4-chlorophenyl ester,  
4-(4-Phenylbutyl)piperazine-1-carboxylic acid 4-chlorophenyl ester,  
4-[2-(2-Hydroxyethoxy)ethyl]piperazine-1-carboxylic acid 4-(4-trifluoromethylphenoxy)phenyl ester,  
4-(1-Ethylpropyl)piperazine-1-carboxylic acid 4-(4-trifluoromethylphenoxy)phenyl ester,  
30 4-Cycloheptylpiperazine-1-carboxylic acid 4-(4-trifluoromethyl-phenoxy)phenyl ester,  
4-Cyclohexylpiperazine-1-carboxylic acid 4-(4-trifluoromethyl-phenoxy)phenyl ester,  
4-(4-Chlorobenzyl)piperazine-1-carboxylic acid 4-(4-trifluoromethylphenoxy)phenyl ester,  
4-(4-Methylbenzyl)piperazine-1-carboxylic acid 4-(4-trifluoromethylphenoxy)phenyl ester,  
4-(4-Methoxybenzyl)piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl  
35 ester,

- 4-(2-Chloro-6-fluoro-benzyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
4-(3-Methoxyphenyl)piperazine-1-carboxylic acid 4-(4-trifluoromethylphenoxy)phenyl ester,  
4-Benzyl-piperazine-1-carboxylic acid 4-(3-chloro-5-trifluoromethyl-pyridin-2-yloxy)phenyl ester,  
5 4-Methyl-piperazine-1-carboxylic acid pyrazol-1-yl ester,  
4-Cyclopentyl-piperazine-1-carboxylic acid pyrazol-1-yl ester,  
4-Phenyl-piperazine-1-carboxylic acid pyrazol-1-yl ester,  
4-Pyridin-2-yl-piperazine-1-carboxylic acid pyrazol-1-yl ester,  
10 4-Pyrimidin-2-yl-piperazine-1-carboxylic acid pyrazol-1-yl ester,  
4-Benzo[1,3]dioxol-5-yl-piperazine-1-carboxylic acid pyrazol-1-yl ester,  
4-Benzyl-piperazine-1-carboxylic acid 4-iodo-pyrazol-1-yl ester,  
4-Cyclopentyl-piperazine-1-carboxylic acid 4-iodo-pyrazol-1-yl ester,  
4-(4-Fluoro-benzyl)-piperazine-1-carboxylic acid 4-iodo-pyrazol-1-yl ester,  
15 4-Phenyl-piperazine-1-carboxylic acid 4-iodo-pyrazol-1-yl ester,  
4-Pyridin-2-yl-piperazine-1-carboxylic acid 4-iodo-pyrazol-1-yl ester,  
4-Pyrimidin-2-yl-piperazine-1-carboxylic acid 4-iodo-pyrazol-1-yl ester,  
4-Benzo[1,3]dioxol-5-yl-piperazine-1-carboxylic acid 4-iodo-pyrazol-1-yl ester,  
4-Methyl-1,4-diazepane-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)phenyl ester,  
20 4-Benzyl-1,4-diazepane-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
4-(Tetrahydrofuran-2-ylmethyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
4-Cyclopropylmethyl-piperazine-1-carboxylic acid 4-(3-chloro-5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
25 4-(Tetrahydro-furan-2-ylmethyl)-piperazine-1-carboxylic acid 4-(4-trifluoromethylphenoxy)-phenyl ester,  
4-Cyclohexylmethyl-piperazine-1-carboxylic acid 4-(4-trifluoromethyl-phenoxy)-phenyl ester,  
4-Cyclohexylmethyl-piperazine-1-carboxylic acid 4-(3-chloro-5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
30 4-Cyclopropylmethyl-piperazine-1-carboxylic acid 4-(4-trifluoromethyl-phenoxy)-phenyl ester,  
4-(Tetrahydrofuran-2-ylmethyl)-piperazine-1-carboxylic acid 4-(3-chloro-5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
4-Naphthalen-1-ylmethyl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
35 4-(2-Cyclohexyl-ethyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-

- phenyl ester,  
4-(3-Methoxy-phenyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-  
phenyl ester,  
4-Cyclopropylmethyl-piperazine-1-carboxylic acid 4-[2-(4-chloro-phenyl)-ethylcarbamoyl]-  
5 phenyl ester,  
4-(Tetrahydro-furan-2-ylmethyl)-piperazine-1-carboxylic acid 4-[2-(4-chloro-phenyl)-  
ethylcarbamoyl]-phenyl ester,  
4-(3,4-Dichloro-benzyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-  
phenyl ester,  
10 4-Cyclopropylmethyl-[1,4]diazepane-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-  
phenyl ester,  
4-(2-Pyridin-2-yl-ethyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-  
phenyl ester,  
4-(Pyrazin-2-yl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl es-  
15 ter,  
4-(Benzo-isothiazol-3-yl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-  
phenyl ester,  
4-(5-Chloro-thiophen-2-ylmethyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-  
yloxy)-phenyl ester,  
20 4-(3-Trifluoromethyl-phenyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-  
phenyl ester,  
4-(5-Chloro-2-methyl-phenyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-  
yloxy)-phenyl ester,  
4-(1-Methyl-piperidin-4-ylmethyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-  
25 yloxy)-phenyl ester,  
4-Biphenyl-4-ylmethyl-[1,4]diazepane-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-  
phenyl ester  
4-(5-Dimethylamino-naphthalene-1-sulfonyl)-piperazine-1-carboxylic acid 4-(5-  
trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
30 4-(3-Methoxy-benzyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl  
ester,  
4-(3-Fluoro-benzyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl  
ester,  
4-(3-Trifluoromethyl-pyridin-2-yl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-  
35 yloxy)-phenyl ester,

- 4-(3-Fluorobenzyl)-piperazine-1-carboxylic acid 4-(4,6-dimethyl-pyrimidin-2-ylsulfanyl)-phenyl ester,
- 5-(4-Trifluoromethoxybenzyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylic acid 4-(5-trifluoromethylpyridin-2-yloxy)-phenyl ester,
- 5 4-(2,4-Dimethoxyphenyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,
- 5-Benzyl-2,5-diazabicyclo[2.2.1]heptane-2-carboxylic acid 4-(5-trifluoromethylpyridin-2-yloxy)-phenyl ester,
- 4-Pyrimidin-2-yl-piperazine-1-carboxylic acid 4-(5-chloro-pyridin-2-yloxy)-phenyl ester,
- 10 4-Cyclopropylmethyl-piperazine-1-carboxylic acid 4-(4,4-dimethyl-2,6-dioxo-piperidin-1-yl)-phenyl ester,
- 4-(4-Methoxy-benzyl)-piperazine-1-carboxylic acid 4-(4,4-dimethyl-2,6-dioxo-piperidin-1-yl)-phenyl ester,
- 4-Pyridin-3-ylmethyl-piperazine-1-carboxylic acid 4-(4,4-dimethyl-2,6-dioxo-piperidin-1-yl)-phenyl ester,
- 15 4-(4-Methoxy-benzyl)-piperazine-1-carboxylic acid 4-(2-cyclohexyl-acetyl-amino)-phenyl ester,
- 4-Cyclopropylmethyl-piperazine-1-carboxylic acid 4-(2-cyclohexyl-acetyl-amino)-phenyl ester,
- 4-Pyridin-3-ylmethyl-piperazine-1-carboxylic acid 4-(2-cyclohexyl-acetyl-amino)-phenyl ester,
- 20 4-Cyclopropylmethyl-piperazine-1-carboxylic acid 4-(3,3-dimethyl-butylcarbamoyl)-phenyl ester,
- 4-Pyridin-3-ylmethyl-piperazine-1-carboxylic acid 4-(3,3-dimethyl-butylcarbamoyl)-phenyl ester,
- 4-(4-Methoxy-benzyl)-piperazine-1-carboxylic acid 4-(3,3-dimethyl-butylcarbamoyl)-phenyl ester,
- 25 4-(2-Pyridin-2-yl-acetyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,
- Piperazine-1,4-dicarboxylic acid tert-butyl ester 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,
- 30 Piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester hydrochloride,
- 4-(2-Pyridin-2-yl-acetyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester, and
- 4-(2-Pyridin-4-yl-ethyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester.

Further examples of specific compounds of the invention are :

- Morpholine-4-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
Morpholine-4-carboxylic acid 3-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
Morpholine-4-carboxylic acid 4-(3,5-dichloro-pyridin-2-yloxy)-phenyl ester,  
5 Morpholine-4-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-ylamino)-phenyl ester,  
Morpholine-4-carboxylic acid 4-(3,5-dichloro-pyridin-4-yloxy)-phenyl ester,  
Morpholine-4-carboxylic acid 4-(4-trifluoromethyl-phenoxy)-phenyl ester,  
Morpholine-4-carboxylic acid 4-(2-cyano-5-trifluoromethyl-pyridine-3-yloxy)-phenyl ester,  
Morpholine-4-carboxylic acid 2-benzenesulfonyl-4-(3-chloro-5-trifluoromethyl-pyridine-2-  
10 yloxy)-phenyl ester,  
Morpholine-4-carboxylic acid 4-tert-butoxy-phenyl ester,  
Morpholine-4-carboxylic acid 3-(4-fluorobenzyl)-4-methyl-2-oxo-2H-chromen-7-yl ester,  
Morpholine-4-carboxylic acid 4-phenoxy-phenyl ester,  
Morpholine-4-carboxylic acid 4-(4-chlorobenzoyl)-phenyl ester,  
15 Morpholine-4-carboxylic acid 4-(3-chloro-5-trifluoromethyl)-pyridine-2-yloxy)-phenyl ester,  
Morpholine-4-carboxylic acid 4-[4-(4-chloro-phenyl)-thiazol-2-yl]-phenyl ester,  
Morpholine-4-carboxylic acid 4-pyrrol-1-yl-phenyl ester,  
Morpholine-4-carboxylic acid 4-imidazol-1-yl-phenyl ester,  
Morpholine-4-carboxylic acid 4-(3-chloro-5-trifluoromethyl)-pyridine-2-ylmethyl)-phenyl ester,  
20 Morpholine-4-carboxylic acid 4-trifluoromethylsulfanyl-phenyl ester,  
Morpholine-4-carboxylic acid 4-pentafluoromethyloxy-phenyl ester,  
Morpholine-4-carboxylic acid 4-benzyloxy-phenyl ester,  
Morpholine-4-carboxylic acid 4-benzyl-phenyl ester,  
Morpholine-4-carboxylic acid 4'-cyano-biphenyl-4-yl-ester,  
25 Morpholine-4-carboxylic acid 4'-bromo-biphenyl-4-yl-ester,  
Morpholine-4-carboxylic acid biphenyl-4-yl-ester,  
Morpholine-4-carboxylic acid 4-[3-(4-chlorophenyl)-ureido]-phenyl ester,  
Morpholine-4-carboxylic acid 4-(4-nitro-phenoxy)-phenyl ester,  
Morpholine-4-carboxylic acid 4-heptylsulfanyl-phenyl ester,  
30 Morpholine-4-carboxylic acid 4-butoxy-phenyl ester,  
Morpholine-4-carboxylic acid 4-(4-chloro-benzenesulfonyl)-phenyl ester,  
Morpholine-4-carboxylic acid 4-(4-chloromethyl-thiazol-2-yl)-phenyl ester  
Morpholine-4-carboxylic acid 4-(4,4-dimethyl-2,6-dioxo-piperidin-1-yl)-phenyl ester,  
cis-Morpholine-4-carboxylic acid 4-(1,3-dioxo-octahydro-isoindol-2-yl)-phenyl ester,  
35 Morpholine-4-carboxylic acid 4-(cyclohexanecarbonyl-amino)-phenyl ester,



- Morpholine-4-carboxylic acid 4-(2-cyclohexyl-acetylamino)-phenyl ester,  
cis/trans-Morpholine-4-carboxylic acid 4-[(4-tert-butyl-cyclohexanecarbonyl)-amino]-phenyl ester,  
cis-Morpholine-4-carboxylic acid 4-[(4-tert-butyl-cyclohexanecarbonyl)-amino]-phenyl ester,  
5 trans-Morpholine-4-carboxylic acid 4-[(4-tert-butyl-cyclohexanecarbonyl)-amino]-phenyl ester,  
Morpholine-4-carboxylic acid 4-(3,3-dimethyl-butyrylamino)-phenyl ester,  
Morpholine-4-carboxylic acid 3-benzyl-4-methyl-2-oxo-2H-chromen-7-yl ester,  
Morpholine-4-carboxylic acid 3-(3,4-dichloro-benzyl)-4-methyl-2-oxo-2H-chromen-7-yl ester,  
10 Morpholine-4-carboxylic acid 3-(2-chloro-6-fluoro-benzyl)-4-methyl-2-oxo-2H-chromen-7-yl ester,  
Morpholine-4-carboxylic acid 3-(2,6-dichloro-benzyl)-4-methyl-2-oxo-2H-chromen-7-yl ester,  
Morpholine-4-carboxylic acid 3-(2,6-dichloro-benzyl)-6-chloro-4-methyl-2-oxo-2H-chromen-7-yl ester,  
15 Morpholine-4-carboxylic acid 6-chloro-3-(2-chloro-6-fluoro-benzyl)-4-n-propyl-2-oxo-2H-chromen-7-yl ester,  
Morpholine-4-carboxylic acid 3-(4-methoxy-phenyl)-4-methyl-2-oxo-2H-chromen-7-yl ester,  
Morpholine-4-carboxylic acid 4-methyl-2-oxo-3-phenyl-2H-chromen-7-yl ester,  
Morpholine-4-carboxylic acid 3-(2,5-dimethoxy-phenyl)-4-methyl-2-oxo-2H-chromen-7-yl ester,  
20 ter,  
Morpholine-4-carboxylic acid 3-(3,4-dimethoxy-phenyl)-4-methyl-2-oxo-2H-chromen-7-yl ester,  
Morpholine-4-carboxylic acid 4-(5,7-bis-trifluoromethyl-[1,8]naphthypyridin-2-yloxy)-phenyl ester,  
25 Morpholine-4-carboxylic acid 4-pyrrolidine-1-yl-phenyl ester,  
Morpholine-4-carboxylic acid 4-piperidine-1-yl-phenyl ester,  
Morpholine-4-carboxylic acid 4-morpholine-1-yl-phenyl ester,  
Morpholine-4-carboxylic acid 4-[(6-chloro-pyridine-3-carbonyl)-amino]-phenyl ester,  
Morpholine-4-carboxylic acid 4-[(6-chloro-pyridine-3-carbonyl)-amino]-phenyl ester,  
30 Morpholine-4-carboxylic acid 4-[(pyridine-2-carbonyl)-amino]-phenyl ester,  
2,6-dimethyl-morpholine-4-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester,  
Morpholine-4-carboxylic acid pyrazol-1-yl ester,  
Morpholine-4-carboxylic acid 3-bromo-pyrazol-1-yl ester,  
Morpholine-4-carboxylic acid 4-bromo-pyrazol-1-yl ester,  
35 Morpholine-4-carboxylic acid 5-bromo-pyrazol-1-yl ester,

- Morpholine-4-carboxylic acid 3,4,5-tribromo-pyrazol-1-yl ester,  
Morpholine-4-carboxylic acid 4-chloro-pyrazol-1-yl ester,  
Morpholine-4-carboxylic acid 4-iodo-pyrazol-1-yl ester,  
Morpholine-4-carboxylic acid 3-(4-methoxy-phenyl)-pyrazol-1-yl ester,  
5 Morpholine-4-carboxylic acid 3-(2-methoxy-phenyl)-pyrazol-1-yl ester,  
Morpholine-4-carboxylic acid 3-(4-nitro-phenyl)-pyrazol-1-yl ester,  
Morpholine-4-carboxylic acid 3-(2-fluoro-phenyl)-pyrazol-1-yl ester,  
Morpholine-4-carboxylic acid 3-pyridin-2-yl-pyrazol-1-yl ester,  
Morpholine-4-carboxylic acid 4-phenylsulfanyl-pyrazol-1-yl ester,  
10 Morpholine-4-carboxylic acid 3-thiophen-2-yl-pyrazol-1-yl ester,  
Morpholine-4-carboxylic acid 5-thiophen-2-yl-pyrazol-1-yl ester,  
Morpholine-4-carboxylic acid imidazol-1-yl ester,  
Morpholine-4-carboxylic acid 2-chloro-imidazol-1-yl ester,  
Morpholine-4-carboxylic acid 2-bromo-imidazol-1-yl ester,  
15 Morpholine-4-carboxylic acid 2-iodo-imidazol-1-yl ester,  
Morpholine-4-carboxylic acid 2-methyl-imidazol-1-yl ester,  
Morpholine-4-carboxylic acid 2-phenylsulfanyl-imidazol-1-yl ester,  
Morpholine-4-carboxylic acid 2-(4-methoxy-phenyl)-imidazol-1-yl ester,  
Morpholine-4-carboxylic acid 2-(4-fluoro-phenyl)-imidazol-1-yl ester,  
20 Morpholine-4-carboxylic acid 2-thiophen-2-yl-imidazol-1-yl ester,  
Morpholine-4-carboxylic acid 2-pyridin-2-yl-imidazol-1-yl ester,  
Morpholine-4-carboxylic acid 2,5-dichloro-imidazol-1-yl ester,  
Morpholine-4-carboxylic acid 4-bromo-2,5-dichloro-imidazol-1-yl ester,  
Morpholine-4-carboxylic acid 4-bromo-2-chloro-imidazol-1-yl ester,  
25 Morpholine-4-carboxylic acid 5-(4-methoxy-phenyl)-imidazol-1-yl ester,  
Morpholine-4-carboxylic acid 5-(4-fluoro-phenyl)-imidazol-1-yl ester,  
Morpholine-4-carboxylic acid 5-thiophen-2-yl-imidazol-1-yl ester,  
Morpholine-4-carboxylic acid 5-pyridin-2-yl-imidazol-1-yl ester,  
Morpholine-4-carboxylic acid 4-trifluoromethyl-pyrimidin-2-yl ester,  
30 Morpholine-4-carboxylic acid 4-trifluoromethyl-pyrimidin-2-yl ester,  
Morpholine-4-carboxylic acid imidazol-1-yl ester,  
Morpholine-4-carboxylic acid 2-bromo-imidazol-1-yl ester,  
Morpholine-4-carboxylic acid 2-chloro-imidazol-1-yl ester,  
Morpholine-4-carboxylic acid 2-phenylsulfanyl-imidazol-1-yl ester,  
35 Morpholine-4-carboxylic acid 2-(4-methoxy-phenyl)-imidazol-1-yl ester,

- Morpholine-4-carboxylic acid 4-bromo-pyrazol-1-yl ester,  
 Morpholine-4-carboxylic acid 4-iodo-pyrazol-1-yl ester,  
 Morpholine-4-carboxylic acid 3,4,5-tribromo-pyrazol-1-yl ester,  
 Morpholine-4-carboxylic acid 3-(4-methoxy-phenyl)-pyrazol-1-yl ester,  
 5 Morpholine-4-carboxylic acid 3-thiophen-2-yl-pyrazol-1-yl ester,  
 Morpholine-4-carboxylic acid pyrazol-1-yl ester, and  
 1-Oxo-1 $\lambda$ <sup>4</sup>-thiomorpholine-4-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

Further examples of specific compounds of the invention are :

- 10 Methyl-o-tolyl-carbamic acid 4-iodo-pyrazol-1-yl ester,  
 Methyl-m-tolyl-carbamic acid 4-iodo-pyrazol-1-yl ester, Methyl-p-tolyl-carbamic acid 4-iodo-pyrazol-1-yl ester, (3-Chloro-phenyl)-methyl-carbamic acid 4-iodo-pyrazol-1-yl ester, (3-Fluoro-phenyl)-methyl-carbamic acid 4-iodo-pyrazol-1-yl ester, 4-(3-Trifluoromethyl-pyridin-2-yl)-piperazine-1-carboxylic acid 4-iodo-pyrazol-1-yl ester,  
 15 2,6-Dimethyl-morpholine-4-carboxylic acid 4-iodo-pyrazol-1-yl ester,  
 Thiomorpholine-4-carboxylic acid 4-iodo-pyrazol-1-yl ester,  
 3,5-Dimethyl-morpholine-4-carboxylic acid 4-iodo-pyrazol-1-yl ester,  
 Piperidine-1-carboxylic acid 4-iodo-pyrazol-1-yl ester,  
 Methyl-o-tolyl-carbamic acid 2-chloro-imidazol-1-yl ester,  
 20 (3-Fluoro-phenyl)-methyl-carbamic acid 2-chloro-imidazol-1-yl ester, and  
 Methyl-phenyl-carbamic acid 5-phenylsulfanyl-pyrazol-1-yl ester.

Further examples of compounds of the invention are :

- N-Methyl-N-phenyl-5-hexylsulfanyl-3-p-tolyl-[1,2,4]triazole-1-carboxamide,  
 25 N-Methyl-N-phenethyl-5-ethyl-3-(4-chlorophenyl)-[1,2,4]triazole-1-carboxamide,  
 [3-(4-Chlorophenyl)-5-methylsulfanyl-[1,2,4]triazol-1-yl]-morpholin-4-yl-methanone,  
 N,N-Dimethyl-5-methylsulfanyl-3-naphthalen-2-yl-[1,2,4]triazole-1-carboxamide,  
 N,N-Dimethyl-3-(4-chloro-phenyl)-5-ethylsulfanyl-[1,2,4]triazole-1-carboxamide, and  
 N,N-Dimethyl-3-biphenyl-4-yl-5-methylsulfanyl-[1,2,4]triazole-1-carboxamide.

30

The present invention also encompasses compounds of formulae I-XXXXVIII, which possess a range of pharmaceutically desirable properties.

In one embodiment, the invention is concerned with compounds of formulae I-XXXXVIII, which have a solubility in water of at least 0.5 mg/L, preferably at least 2 mg/L, more prefer-

able at least 10 mg/L, more preferable at least 50 mg/L and most preferable at least 200 mg/L as determined at 25 °C and pH 7.0.

In another embodiment, the invention is concerned with compounds of formulae I-XXXXVIII, which have a solubility in water of at least 0.5 mg/L, preferably at least 2 mg/L, more preferable at least 10 mg/L, more preferable at least 50 mg/L and most preferable at least 200 mg/L as determined at 25 °C and pH 2.0.

In another embodiment, the invention is concerned with compounds of formulae I-XXXXVIII, which have an  $IC_{50}$  value of no greater than 5  $\mu$ M as determined by the assay 3190.2 or 3180.1 disclosed herein.

In another embodiment, the invention is concerned with compounds of formulae I-XXXXVIII, which have an  $IC_{50}$  value of less than 1  $\mu$ M, preferably less than 500 nM, preferably less than 100 nM, preferably less than 50 nM, more preferable less than 25 nM, more preferable less than 10nM and even more preferable less than 5 nM as determined by the assay 3190.2 or 3180.1 disclosed herein.

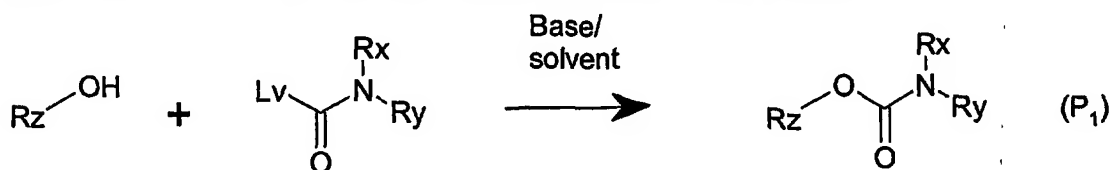
In another embodiment, the invention is concerned with compounds of formulae I-XXXXVIII, which are ionized at pH 7.0.

In another embodiment, the invention is concerned with compounds of formulae I-XXXXVIII, which have a  $pK_a$  in the range from 8 to 12, preferable from 9 to 12, more preferable from 10 to 12.

In another embodiment, the invention is concerned with compounds of formulae I-XXXXVIII, which have a molar weight of no greater than 1000 D.

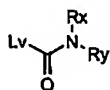
In another embodiment, the invention is concerned with compounds of formulae I-XXXXVIII, which have a molar weight of less than 750 D, preferably less than 500 D, more preferable less than 400 D, more preferable less than 300D and even more preferably less than 250 D.

In another aspect the invention is concerned with a process for the preparation of a compound of formulae I-XXXXVIII or their pharmaceutically acceptable salts, which process comprises reacting the appropriate alcohol, R<sub>z</sub>-OH, with the appropriate carbamoylating reagent, Lv-C(=O)-NR<sub>x</sub>R<sub>y</sub>, in a solvent according to the reaction scheme P<sub>1</sub>

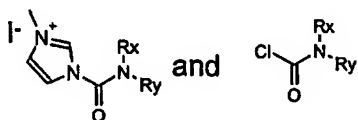


and isolating the disubstituted carbamate product.

In one embodiment, the invention is concerned with process P<sub>1</sub>, wherein said carbamoylating reagent



is selected from the group consisting of



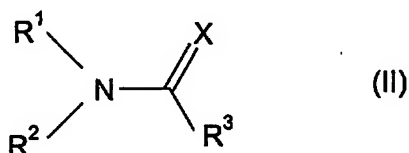
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In another embodiment, the invention is concerned with the process of scheme P<sub>1</sub>, wherein said solvent is selected from the group consisting of tetrahydrofurane, dimethylformamide and N-methylpyrrolidone.

In another embodiment, the invention is concerned with the process of scheme P<sub>1</sub>, wherein  
10 said base is selected from the group consisting of triethylamine, N,N-diisopropyl-N-ethylamine and DABCO.

In another aspect the invention is concerned with a process for the preparation of a compound according to the general formula

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wherein R<sup>1</sup> is selected from C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl and C<sub>3-10</sub>-cycloalkyl, each of which is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, oxo, halogen, amino, cyano and nitro; and

20

R<sup>2</sup> is selected from C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl, each of which is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl is op-

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tionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl is optionally substituted  
5 with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino,  
10 cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, perhalomethyl and perhalomethoxy; and

wherein R<sup>2</sup> is optionally covalently bound to R<sup>1</sup> by an ether, thioether, C-C or C-N bond, to form a ring system with the N-atom to which R<sup>1</sup> and R<sup>2</sup> are bound; and

15 R<sup>3</sup> is selected from hydroxy, sulfanyl, sulfo, amino, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl, each of which is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-  
20 heterocyclyl and C<sub>3-10</sub>-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl is optionally substituted with one or more substituents independently selected  
25 from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-  
30 heterocyclyl and C<sub>3-10</sub>-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, perhalomethyl and perhalomethoxy; and  
35 X is O or S; or

a compound according to any one of formulae III-XXXXVIII; or

a pharmaceutically acceptable salt thereof;

5

said process comprising the treatment of the appropriate amine,  $R^1\text{-NH-R}^2$ , with the appropriate acylating reagent,  $\text{Y-C(=X)-R}^3$ , in a solvent and in the presence of a base according to the reaction scheme  $P_2$



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In one embodiment, the invention is concerned with the process of scheme  $P_2$ , wherein Y is Cl.

In another embodiment, the invention is concerned with the process of scheme  $P_2$ , wherein  $R^3$  is an aryloxy group.

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In another embodiment, the invention is concerned with the process of scheme  $P_2$ , wherein said solvent is selected from the group consisting of diethyl ether, tetrahydrofuran and dichloromethane.

In another embodiment, the invention is concerned with the process of scheme  $P_2$ , wherein said base is selected from the group consisting of trimethylamine, triethylamine, ethyl-

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diisopropyl-amine and 1,4-diazabicyclo[2.2.2]octane.

In another embodiment, the invention is concerned with the process of scheme  $P_2$ , wherein said base is present as a functionality in one or both of the substituents  $R^1$  and  $R^2$ , thus forming a salt with the acid H-Y.

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In another aspect the invention is concerned with a pharmaceutical composition comprising a compound of formulae I-XXXXVIII or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

In one embodiment the invention is concerned with a pharmaceutical composition, wherein said composition is in unit dosage form, comprising from about 0.05 to about 2000 mg,

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preferably from about 0.1 to about 500 mg and even more preferable from about 1.0 to about 100 mg of a compound of formulae I-XXXXVIII or a pharmaceutically acceptable salt thereof.

In another embodiment the invention is concerned with a pharmaceutical composition for use as a medicament for inhibiting the lipolytic activity of hormone-sensitive lipase against

triacylglycerols, diacylglycerols, cholesterol acyl esters or steroid acyl esters, said composition comprising a compound of any one of formulae I-XXXXVIII or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

- 5 In another embodiment the invention is concerned with a pharmaceutical composition for oral, nasal, transdermal, pulmonal, or parenteral administration.

In another aspect the invention is concerned with use of a compound according to any one of formulae I-XXXXVIII for preparation of a medicament for inhibition of the lipolytic activity of  
10 hormone-sensitive lipase against triacylglycerols, diacylglycerols, cholesterol acyl esters or steroid acyl esters.

In one embodiment the invention is concerned with said use, wherein a further antidiabetic, antiobesity, antihypertensive or appetite regulating drug is used.

- 15 In another aspect the invention is concerned with use of a compound according to any one of formulae I-XXXXVIII for the preparation of a medicament for the treatment of any disorder where it is desirable to

modulate the plasma level of free fatty acids, glycerol, LDL-cholesterol, HDL-cholesterol, insulin and/or glucose; and/or  
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modulate intracellular triacylglycerol and cholesterol ester stores, intracellular level of fatty acids, fatty acid esters such as diacylglycerols, phosphatidic acids, long chain acyl-CoA's as well as citrate or malonyl-CoA; and/or  
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increase insulin sensitivity in adipose tissue, skeletal muscle, liver or pancreatic  $\beta$  cells; and/or

modulate insulin secretion from pancreatic  $\beta$  cells.  
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In one embodiment the invention is concerned with said use, wherein said disorder is selected from the group consisting of insulin resistance, diabetes type 1 and 2, metabolic syndrome X, impaired glucose tolerance, hyperglycemia, dyslipidemia, obesity, abnormalities of lipoprotein metabolism and any combination thereof.  
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In another aspect the invention is concerned with use of a compound according to any one of formulae I-XXXXVIII or a pharmaceutically acceptable salt thereof for the preparation of a medicament.

- 5 In another aspect the invention is concerned with a method of treating a disorder of a patient where modulation of the activity of hormone-sensitive lipase is desired, the method comprising administering to said patient an effective amount of a compound according to any one of formulae I-XXXXVIII or a pharmaceutically acceptable salt thereof.
- In one embodiment the invention is concerned with said method, wherein said administration
- 10 is carried out by the oral, nasal, transdermal, pulmonal, or parenteral route.
- In another embodiment the invention is concerned with said method, wherein said disorder is selected from the group consisting of insulin resistance, diabetes type 1 and 2, metabolic syndrome X, impaired glucose tolerance, hyperglycemia, dyslipidemia, obesity, abnormalities of lipoprotein metabolism and any combination thereof.
- 15 In another embodiment the invention is concerned with said method, wherein a further antidiabetic, antiobesity, antihypertensive or appetite regulating drug is administered to the patient.

The present invention also encompasses pharmaceutically acceptable salts of the present

20 compounds. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable base addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, nitric acids and the like. Representative exam-

25 ples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids, sul-

30 phates, nitrates, phosphates, perchlorates, borates, acetates, benzoates, hydroxynaphthoates, glycerophosphates, ketoglutarates and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977, 66, 2, which is incorporated herein by reference. Exam-

35 ples of metal salts include lithium, sodium, potassium, magnesium, zinc, calcium salts and the like. Examples of amines and organic amines include ammonium, methylamine, di-

methylamine, trimethylamine, ethylamine, diethylamine, propylamine, butylamine, tetramethylamine, ethanolamine, diethanolamine, triethanolamine, meglumine, ethylenediamine, choline, N,N'-dibenzylethylenediamine, N-benzylphenylethylamine, N-methyl-D-glucamine, guanidine and the like. Examples of cationic amino acids include lysine, arginine, histidine and the like.

The pharmaceutically acceptable salts are prepared by reacting the compound of formulae I-XXXXVIII with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in solvents like ether, THF, methanol, t-butanol, dioxane, isopropanol, ethanol etc. Mixture of solvents may be used. Organic bases like lysine, arginine, diethanolamine, choline, guanidine and their derivatives etc. may also be used. Alternatively, acid addition salts wherever applicable are prepared by treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid, salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and the like in solvents like ethyl acetate, ether, alcohols, acetone, THF, dioxane etc. Mixture of solvents may also be used.

The stereoisomers of the compounds forming part of this invention may be prepared by using reactants in their single enantiomeric form in the process wherever possible or by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional methods. Some of the preferred methods include use of microbial resolution, enzymatic resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, and the like wherever applicable or chiral bases such as brucine, (R)- or (S)-phenylethylamine, cinchona alkaloids and their derivatives and the like. Commonly used methods are compiled by Jaques et al in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981). More specifically the compound of formula I may be converted to a 1:1 mixture of diastereomeric amides by treating with chiral amines, aminoacids, aminoalcohols derived from aminoacids; conventional reaction conditions may be employed to convert acid into an amide; the diastereomers may be separated either by fractional crystallization or chromatography and the stereoisomers of compound of formulae I-XXXXVIII may be prepared by hydrolysing the pure diastereomeric amide.

Various polymorphs of compound of general formulae I-XXXXVIII forming part of this invention may be prepared by crystallization of compound of formulae I-XXXXVIII under different conditions. For example, using different solvents commonly used or their mixtures for recryst-

tallization; crystallizations at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming active pharmacological substances. In general, such prodrugs will be functional derivatives of the present compounds, which are readily convertible in vivo into the required compound of the formulae I-XXXXVIII. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The invention also encompasses active metabolites of the present compounds. The invention also relates to pharmaceutical compositions comprising, as an active ingredient, at least one compound of the formula I or any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers or diluents.

Furthermore, the invention relates to the use of compounds of the general formulae I-XXXXVIII or their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts or pharmaceutically acceptable solvates thereof for the preparation of a pharmaceutical composition for the treatment and/or prevention of disorders where a decreased level of plasma FFA is desirable, such as the conditions mentioned above.

In another aspect, the present invention relates to a method of treating and/or preventing type 2 diabetes, insulin resistance, metabolic syndrome X, impaired glucose tolerance, dyslipidemia and abnormalities of lipoprotein metabolism.

In a still further aspect, the present invention relates to the use of one or more compounds of the general formulae I-XXXXVIII, or pharmaceutically acceptable salts thereof, for the preparation of a pharmaceutical composition for the treatment and/or prevention of type 2 diabetes, insulin resistance, metabolic syndrome X, impaired glucose tolerance, dyslipidemia and abnormalities of lipoprotein metabolism.

In a still further aspect, the present compounds are useful for the delaying or prevention of the progression from impaired glucose tolerance to type 2 diabetes.

In a still further aspect, the present compounds are useful for the delaying or prevention of the progression from non-insulin requiring type 2 diabetes to insulin requiring type 2 diabetes.

In another aspect, the present compounds reduce triglyceride levels and are accordingly useful for the treatment and/or prevention of ailments and disorders such as diabetes and/or obesity.

In still another aspect, the compounds of general formulae I-XXXXVIII are useful for the treatment of hyperglycemia, elevated HbA<sub>1c</sub> level, hyperinsulinemia, type 1.5 diabetes, latent autoimmune diabetes in adults, maturity onset diabetes, beta-cell apoptosis, hemochromatosis induced diabetes, impaired glucose tolerance, impaired fasting glucose, metabolic syndrome X, insulin resistance, impaired lipid tolerance, cystic fibrosis related diabetes, polycystic ovarian syndrome, and gestational diabetes.

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In still another aspect, the compounds of general formulae I-XXXXVIII are useful for the treatment of obesity, dyslipidemia, diabetic dyslipidemia, hyperlipidemia, hypertriglyceridemia, hyperlipoproteinemia, hypercholesterolemia, hypertension, essential hypertension, acute hypertensive emergency, arteriosclerosis, atherosclerosis, restenosis, intermittent claudication (atherosclerosis obliterans), cardiovascular disease, cardiomyopathy, cardiac hypertrophy, left ventricular hypertrophy, coronary artery disease, early coronary artery disease, heart insufficiency, exercise tolerance, chronic heart failure, mild chronic heart failure, arrhythmia, cardiac dysrhythmia, syncope, heart attack, myocardial infarction, Q-wave myocardial infarction, stroke, acute coronary syndrome, angina pectoris, unstable angina, cardiac bypass reocclusion, diastolic dysfunction, systolic dysfunction, non-Q-wave cardiac necrosis, catabolic changes after surgery, acute pancreatitis, and irritable bowel syndrome

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In still another aspect, the compounds of general formulae I-XXXXVIII may be useful for the treatment of diabetic retinopathy, background retinopathy, preproliferative retinopathy, proliferative retinopathy, macular edema, cataracts, nephropathy, nephrotic syndrome, diabetic nephropathy, microalbuminuria, macroalbuminuria, neuropathy, diabetic neuropathy, distal symmetrical sensorimotor polyneuropathy, and diabetic autonomic neuropathy.

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In still another aspect, the compounds of general formulae I-XXXXVIII are useful for increasing the number of beta-cells in a patient, increasing the size of beta-cells in a patient or stimulating beta-cell proliferation, modulating beta-cell function and insulin secretion in a patient in need thereof, which method comprises administration of an effective amount of a compound of formulae I-XXXXVIII to a patient in need thereof.

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The compounds of the invention are also believed to be useful for reducing body weight in a patient in need thereof.

The compounds of the invention are also believed to be useful Use for weight neutral treatment of above mentioned diseases.

- 5 The compounds of the invention are also believed to be useful for redistributing fat in a patient in need thereof.

The compounds of the invention are also believed to be useful for redistributing central fat in a patient in need thereof.

- 10 The compounds of the invention are also believed to be useful for reducing or preventing central obesity.

The compounds of the invention are also believed to be useful for reducing postprandial serum lipid excursions.

The compounds of the invention are also believed to be useful for the treatment of fatty acid oxidation disorders such as MCAD.

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In still another aspect, the compounds of general formulae I-XXXXVIII are believed to be useful for the treatment of a disease, condition or disorder wherein cholesterol is a precursor. Such diseases, conditions or disorders may relate to testosterone, e.g. male contraception, excessive testosterone levels, PCOS and prostate cancer. They may also relate to cortisol or corticotropin, e.g. Cushing disease.

20

The compounds of the invention are also believed to be useful for the treatment of cancer. Thus, the compounds of the general formulae I-XXXXVIII may be useful for the treatment of insulinoma (pancreatic islet cell tumors), e.g. malignant insulinomas and multiple insulinomas, adipose cell carcinomas, e.g. lipocarcinoma.

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The compounds of the invention are also believed to be useful for the treatment of pheochromocytoma and other diseases with increased catecholamine secretion.

The compounds of the invention are also believed to be useful for the treatment of prostate cancer, e.g. adenocarcinoma.

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In still another aspect, the compounds of general formulae I-XXXXVIII may be useful for the treatment of hepatic steatosis.

In still another aspect, the compounds of general formulae I-XXXXVIII may be useful for the treatment of cirrhosis.

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In still another aspect, the compounds of general formulae I-XXXXVIII may be useful for the treatment of AIDS or an AIDS related diseases, condition or disorders

In still another aspect, the compounds of general formulae I-XXXXVIII may be useful for the treatment of lipodystrophy

In still another aspect, the compounds of general formulae I-XXXXVIII may be useful for the treatment of lactic acidosis.

5 In yet another aspect, the compounds of the present invention are expected to be useful for the treatment of CNS diseases, conditions or disorders.

Thus, the compound of the present invention may be used for the treatment of Parkinsons disease, Alzheimers disease, ADHD (Attention Deficit Hyperactivity Disorder), feeding disorders such as bulimia and anorexia, depression, anxiety, cognitive memory disorders, age  
10 related cognitive decline, mild cognitive impairment and schizophrenia.

In yet another aspect, the compounds of the present invention may be useful for the treatment of inflammatory disorders, e.g. rheumatoid arthritis, psoriasis, systemic inflammatory response syndrome, sepsis and the like.

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The present compounds may also be administered in combination with one or more further pharmacologically active substances eg., selected from antiobesity agents, antidiabetics, antihypertensive agents, agents for the treatment and/or prevention of complications resulting  
20 from or associated with diabetes and agents for the treatment and/or prevention of complications and disorders resulting from or associated with obesity.

Thus, in a further aspect of the invention the present compounds may be administered in combination with one or more antiobesity agents or appetite regulating agents.

Such agents may be selected from the group consisting of CART (cocaine amphetamine regulated transcript) agonists, NPY (neuropeptide Y) antagonists, MC4 (melanocortin 4)  
25 agonists, orexin antagonists, TNF (tumor necrosis factor) agonists, CRF (corticotropin releasing factor) agonists, CRF BP (corticotropin releasing factor binding protein) antagonists, urocortin agonists,  $\beta 3$  agonists, MSH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone) antagonists, CCK (cholecystokinin) agonists, serotonin  
30 re-uptake inhibitors, serotonin and noradrenaline re-uptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT (serotonin) agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone releasing compounds, TRH (thyreotropin releasing hormone) agonists, UCP 2 or 3 (uncoupling protein 2 or 3) modulators, leptin agonists, DA  
agonists (bromocriptin, dorexin), lipase/amylase inhibitors, RXR (retinoid X receptor) modu-  
35 lators or TR  $\beta$  agonists.

In one embodiment of the invention the antiobesity agent is leptin.

In another embodiment the antiobesity agent is dexamphetamine or amphetamine.

In another embodiment the antiobesity agent is fenfluramine or dexfenfluramine.

In still another embodiment the antiobesity agent is sibutramine.

5 In a further embodiment the antiobesity agent is orlistat.

In another embodiment the antiobesity agent is mazindol or phentermine.

Suitable antidiabetics comprise insulin, exendin-4, GLP-1 (glucagon like peptide-1) derivatives such as those disclosed in WO 98/08871 to Novo Nordisk A/S, which is incorporated herein by reference as well as orally active hypoglycaemic agents.

10 The orally active hypoglycaemic agents preferably comprise sulphonylureas, biguanides, meglitinides, glucosidase inhibitors, glucagon antagonists such as those disclosed in WO 99/01423 to Novo Nordisk A/S and Agouron Pharmaceuticals, Inc., GLP-1 agonists, potassium channel openers such as those disclosed in WO 97/26265 and WO 99/03861 to Novo Nordisk A/S which are incorporated herein by reference, DPP-IV (dipeptidyl peptidase-IV)  
15 inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or glycogenolysis, glucose uptake modulators, compounds modifying the lipid metabolism such as antihyperlipidemic agents and antilipidemic agents as HMG CoA inhibitors (statins), compounds lowering food intake, RXR agonists and agents acting on the ATP-dependent potassium channel of the  $\beta$ -cells.

20 In one embodiment of the invention the present compounds are administered in combination with insulin.

In a further embodiment the present compounds are administered in combination with a sulphonylurea eg. tolbutamide, glibenclamide, glipizide or glicazide.

In another embodiment the present compounds are administered in combination with a  
25 biguanide eg. metformin.

In yet another embodiment the present compounds are administered in combination with a meglitinide eg. repaglinide or senaglinide.

In a further embodiment the present compounds are administered in combination with an  $\alpha$ -glucosidase inhibitor eg. miglitol or acarbose.

30 In another embodiment the present compounds are administered in combination with an agent acting on the ATP-dependent potassium channel of the  $\beta$ -cells eg. tolbutamide, glibenclamide, glipizide, glicazide or repaglinide.

Furthermore, the present compounds may be administered in combination with nateglinide.

In still another embodiment the present compounds are administered in combination with an antihyperlipidemic agent or antilipidemic agent eg. cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol or dextrothyroxine.

In a further embodiment the present compounds are administered in combination with more than one of the above-mentioned compounds eg. in combination with a sulphonylurea and metformin, a sulphonylurea and acarbose, repaglinide and metformin, insulin and a sulphonylurea, insulin and metformin, insulin, insulin and lovastatin, etc.

Furthermore, the present compounds may be administered in combination with one or more antihypertensive agents. Examples of antihypertensive agents are  $\beta$ -blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, ACE (angiotensin converting enzyme) inhibitors such as benazepril, captopril, alatriopril, enalapril, fosinopril, lisinopril, quinapril and ramipril, calcium channel blockers such as nifedipine, felodipine, nicardipine, isradipine, nimodipine, diltiazem and verapamil, and  $\alpha$ -blockers such as doxazosin, urapidil, prazosin and terazosin. Further reference can be made to Remington: The Science and Practice of Pharmacy, 19<sup>th</sup> Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

It should be understood that any suitable combination of the compounds according to the invention with one or more of the above-mentioned compounds and optionally one or more further pharmacologically active substances are considered to be within the scope of the present invention.

The present invention also relates to processes according to reaction schemes P<sub>1</sub> and P<sub>2</sub> for the preparation of the above said novel compounds, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts or pharmaceutically acceptable solvates.

#### **Pharmaceutical compositions.**

The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19<sup>th</sup> Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.



The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred. It will be appreciated that the preferred route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen.

Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules. Where appropriate, they can be prepared with coatings such as enteric coatings or they can be formulated so as to provide controlled release of the active ingredient such as sustained or prolonged release according to methods well-known in the art.

Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

Pharmaceutical compositions for parenteral administration include sterile aqueous and non-aqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Depot injectable formulations are also contemplated as being within the scope of the present invention.

Other suitable administration forms include suppositories, sprays, ointments, cremes, gels, inhalants, dermal patches, implants etc.

The therapeutic dose of the compound will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those skilled in the art. The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art. In one embodiment the composition in unit dosage form, comprises from about 0.05 to about 2000 mg, preferably from about 0.1 to about 500 mg of the compound of formula I pharmaceutically acceptable salt thereof.

In a still further embodiment the pharmaceutical composition is for oral, nasal, transdermal, pulmonal, or parenteral administration.

- 5 For parenteral routes, such as intravenous, intrathecal, intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration.

The compounds of this invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. One example is an acid addition salt of a compound having  
10 the utility of a free base. When a compound of the invention contains a free base such salts are prepared in a conventional manner by treating a solution or suspension of a free base of the compound with a chemical equivalent of a pharmaceutically acceptable acid, for example, inorganic and organic acids. Representative examples are mentioned above. Physiologically acceptable salts of a compound with a hydroxy group include the anion of said compound in combination with a suitable cation such as sodium or ammonium ion.  
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For parenteral administration, solutions of the present compounds in sterile aqueous solution, aqueous propylene glycol or sesame or peanut oil may be employed. Such aqueous solutions should be suitable buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.  
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Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution  
25 and various organic solvents. Examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatine, lactose, terra alba, sucrose, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include  
30 any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents.

The pharmaceutical compositions formed by combining the compounds of the invention and the pharmaceutically acceptable carriers are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

5

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of the active ingredient, and which may include a suitable excipient. These formulations may be in the form of powder or granules, as a solution or suspension in an aqueous or non-aqueous liquid, or as  
10 an oil-in-water or water-in-oil liquid emulsion.

If a solid carrier is used for oral administration, the preparation may be tableted, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g.

15 If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

A typical tablet which may be prepared by conventional tableting techniques may contain:

## Core:

	Active compound (as free compound or salt thereof)	5 mg
	Colloidal silicon dioxide (Aerosil)	1.5 mg
	Cellulose, microcryst. (Avicel)	70 mg
5	Modified cellulose gum (Ac-Di-Sol)	7.5 mg
	Magnesium stearate	q.s.

## Coating:

	HPMC approx.	9 mg
10	*Mywacett 9-40 T approx.	0.9 mg

\*Acylated monoglyceride used as plasticizer for film coating.

15 The compounds of the invention may be administered to a patient which is a mammal, especially a human in need thereof. Such mammals include also animals, both domestic animals, e.g. household pets, and non-domestic animals such as wildlife.

20 In a further aspect of the invention the present compounds may be administered in combination with further pharmacologically active substances e.g. an antidiabetic or other pharmacologically active material, including other compounds for the treatment and/or prevention of insulin resistance and diseases, wherein insulin resistance is the pathophysiological mechanism.

25 Furthermore, the compounds according to the invention may be administered in combination with antiobesity agents or appetite regulating agents.

**EXAMPLES.****General Methods**

5 All reactions involving air-sensitive reagents were performed under nitrogen using syringe-septum cap techniques. The glassware were dried by heating with a heath-gun.  $\text{MgSO}_4$  were used to dry solutions. Solvents were removed *in vacuo* by rotary evaporation. Melting points were recorded on a Büchi 535, Bruker AMX 400 and Bruker DRX 300 instruments were used  
10 to record  $^1\text{H}$  NMR spectra at 400 and 300 MHz respectively with tetramethylsilane (TMS) as internal standard. Coupling constants (*J*) are given in Hz.

**Materials**

Test compounds were synthesized or when commercially available they were purchased  
15 from Specs, Maybridge, Comgenex, Peakdale or Bionet. For the synthesized compounds the procedure for synthesis and measured characteristics of the compound are stated in the example. All compounds for which no synthesis procedure is stated in the examples are commercially available and have been purchased, or were prepared by standard methods described in the literature.

20 *N*-methyl-phenethylcarbamoyl chloride was prepared from *N*-methyl-phenethylamine and phosgene using triethylamine as a base in dichloromethane. 1-Methyl-3-(morpholine-4-carbonyl)-3H-imidazol-1-ium iodide, 3-(3,4-dihydro-2H-quinoline-1-carbonyl)-1-methyl-3H-imidazol-1-ium iodide and 1-methyl-3-(methyl-phenyl-carbamoyl)-3H-imidazol-1-ium iodide  
25 was prepared as described by Batey, R.A., Tetrahedron Lett. 39, 1998, 6267.

1-Hydroxypyrazole was prepared as described in Begtrup, Vedsø, J. Chem. Soc. Perkin Trans 1, 1995, 243. 1-hydroxy-4-bromopyrazole was prepared as described in Balle et al., J. Org. Chem. 64, 1999, 5366. 1-hydroxy-3-(4-methoxyphenyl)pyrazole was prepared as described in Eskildsen et al., J. Org. Chem. 2001 (in press). 1-hydroxyimidazole was prepared  
30 as described in Eriksen et al., J. Org. Chem. 63, 1998, 12. 1-hydroxy-1,2,3-triazole was prepared as described in Uhlmann et al., J. Org. Chem. 62, 1997, 9177.

2-Piperidin-4-ylmethyl-1,2,3,4-tetrahydro-isoquinoline, cyclohexyl-methyl-piperidin-4-ylmethyl-amine, methyl-phenethyl-piperidine-4-ylmethyl-amine, ethyl-piperidin-4-ylmethyl-

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piperidin-4-ylmethylamine, benzyl-methyl-piperidin-4-ylmethyl-amine, benzyl-ethyl-piperidin-4-ylmethyl-amine, methyl-piperidin-4-ylmethyl-piperidin-3-ylmethyl-amine, 1-piperidin-4-ylmethyl-piperidin-4-ol, 2-piperidin-4-ylmethyl-2,3-dihydro-1H-isoindole, cyclopropylmethyl-piperidin-4-ylmethyl-amine was prepared from 4-formylpiperidine-1-carboxylic acid *tert*-butyl ester prepared as described by Ting, P. C. (Bioorg, Med. Chem. Lett, 11, 4, 491, 2001) and an appropriate amine by a reductive amination (general procedure 19).

Benzylpiperidine-4-yl-amine, methyl-piperidin-4-yl-(2-pyridin-2-yl-ethyl)-amine, cyclohexyl-methyl-piperidin-4-yl-amine, Isopropyl-methyl-piperidin-4-yl-amine, methyl-phenethyl-piperidin-4-yl-amine, methyl-piperidin-4-yl-pyridin-3-ylmethyl-amine, was prepared from 4-oxopiperidine-1-carboxylic acid *tert*-butyl ester by a standard reductive amination procedure as described by Mattson R. J. (J. Org. Chem. 55, 2552, 1990).

Cyclopropyl-piperidin-4-yl-pyridin-4-ylmethyl-amine was prepared from 4-(cyclopropyl-pyridin-4-ylmethyl-amino)-piperidine-1-carboxylic acid *tert*-butyl ester by a classical N-deprotection reaction (HCl (g) in diethyl ether or ethanol). 4-(Cyclopropyl-pyridin-4-ylmethyl-amino)-piperidine-1-carboxylic acid *tert*-butyl ester was prepared from 4-cyclopropylamino-piperidine-1-carboxylic acid *tert*-butyl ester and pyridine-4-yl-acetaldehyde by a classical reductive amination procedure as described by Mattson R. J. 4-Cyclopropylamino-piperidine-1-carboxylic acid *tert*-butyl ester was prepared from cyclopropylamine and 4-oxopiperidine-1-carboxylic acid *tert*-butyl ester by a standard reductive amination procedure as described by Mattson R. J. Cyclopropyl-(2-fluoro-benzyl)-piperidin-4-yl-amine, cyclopropyl-piperidin-4-yl-pyridin-3-ylmethyl-amine, cyclopropylmethyl-piperidin-4-yl-pyridin-3-ylmethyl-amine and cyclopropylmethyl-piperidin-4-yl-pyridin-4-ylmethyl-amine was prepared by a procedure similar to the one described for cyclopropyl-piperidin-4-yl-pyridin-4-ylmethyl-amine.

Chloroformates were synthesized from the appropriate phenols and phosgene or a phosgene substitute like e.g. trichloromethyl chloroformate as described in Konakahara, Ozaki, Sato, Gold, Synthesis 1993 (1) 103-106, except that the crude product was separated from the diisopropylethylamine hydrochloride by extraction with diethyl ether rather than with THF.

Non-commercial N-monosubstituted piperazines were prepared by alkylation (alkylation procedure as described in e.g. Masaguer, Ravina, Tetrahedron Lett. 1996, 37 (29) 5171-5174) of 1-Boc-piperazine, and subsequent removal of the Boc group under acidic conditions, e.g.

by heating in a mixture of hydrochloric acid and ethanol. N-Monosubstituted homopiprazines and N-monosubstituted 2,5-diazabicyclo[2.2.1]heptanes were prepared in a similar manner.

Thin layer chromatography was performed on Merck DC-Alufolien, silica gel 60 F<sub>254</sub> and components were visualized by UV<sub>254</sub>. Flash chromatography was performed using silica gel Merck 60 size 0.04-0-063 mm and a Quad 12/25 flash system.

#### **Preparative HPLC (Method A).**

The system consists of two Gilson 322 pumps equipped with 30 ml pump heads. A Gilson 215 combined autoinjector and fraction collector performs injection and fraction collection. Detection is performed with a Gilson Diode array detector.

Separation is performed on Waters Xterra columns 19.8 mm \* 100 mm, flow rate 25 ml/min. The most widely used gradient starts at 10 % acetonitrile in water and ends after 11 min on 100 % acetonitrile, the system is buffered by 0.01% TFA. In special cases the gradient is altered to fit the separation need.

#### **Preparative HPLC (Method B)**

HPLC Purification:

The following instrumentation is used:

Gilson 306 Pump  
Gilson 806 Manometric module  
Gilson 811C Dynamic mixer  
Gilson UV/VIS-155  
Gilson 202 Fraction collector

The instrument is controlled by Gilson Unipoint software.

The HPLC pump is connected to two eluent reservoirs containing:

A: 0.01% TFA in water

B: 0.01% TFA in acetonitrile

The purification is performed at room temperature by injecting an appropriate volume of the sample (preferably 2 ml) onto the column, which is eluted with a gradient of acetonitrile.

The HPLC conditions and detector settings used are as follows :

Column: Waters Xterra MS C-18 X 19 x 100 mm  
Gradient: 50% - 60% acetonitrile linearly during 12 min at 20 ml/min  
Detection: 210 and 270 nm

**5 Preparative HPLC (method C)**

The system consists of two Gilson 322 pumps equipped with 30 ml pump heads. Gilson manometric module 805. A Gilson 215 combined autoinjector and fraction collector performs injection and fraction collection. Detection is performed with a Gilson Diode array detector 170. A sample contain 25-100 mg of material dissolved in 0.5-2.0 ml of solvent (minimum water concentration: 10%).

Separation is performed on Waters Xterra, RP<sub>18</sub> 7 $\mu$ m, columns 19 mm x 150 mm, flow rate 15 ml/min (sample added with a flow rate of 5 ml/min for about 1 min). The most widely used gradient starts at 5 % acetonitrile in water and ends after 14 min on 95 % acetonitrile. This concentration is maintained for 6 min. The system is buffered with 0.05% TFA. In special cases the gradient is altered to fit the separation need. The pooled fractions are evaporated to dryness in vacuo.

**HPLC-MS.**

The following instrumentation was used:

- Hewlett Packard series 1100 G1312A Bin Pump
- Hewlett Packard series 1100 Column compartment
- Hewlett Packard series 1100 G13 15A DAD diode array detector
- Hewlett Packard series 1100 MSD

The instrument was controlled by HP Chemstation software.

The HPLC pump was connected to two eluent reservoirs containing:

A: 0.01% TFA in water  
B: 0.01% TFA in acetonitrile

The analysis was performed at 40 °C by injecting an appropriate volume of the sample (preferably 1  $\mu$ l) onto the column, which is eluted with a gradient of acetonitrile.



The HPLC conditions, detector settings and mass spectrometer settings which were used are as follows :

Column	Waters Xterra MS C-18 X 3 mm id
Gradient	10% - 100% acetonitrile linear during 7.5 min at 1.0ml/min
Detection	210 nm (analogue output from DAD)
MS	Ionisation mode API-ES, Scan 100-1000 amu step 0.1 amu

5

#### General procedure 1

The phenol (1.0 mmol) was dissolved in tetrahydrofuran (15 ml) in a glass screw cap vessel, 1,4-diazabicyclo[2.2.2]octane (DABCO) (2.0 mmol) was added together with the respective carbamoyl chloride (2.0 mmol) at room temperature. The reaction mixture was shaken for 16  
10 hours and poured into ethyl acetate (20 ml) and aqueous citric acid (5%; 20 ml). The organic phase was dried and evaporated to give the crude product.

#### General procedure 2

The phenol (1.0 mmol) was dissolved in acetonitrile (15 ml) in a glass screw cap vessel. Triethylamine (1.0 mmol) was added together with the respective 1-methyl-3*H*-imidazol-1-  
15 ium iodide (1.0 mmol) at room temperature. The reaction mixture was shaken for 16-48 hours at 80 °C, cooled to room temperature and evaporated. The evaporated reaction mixture was dissolved in dichloromethane (20 ml) and extracted with aqueous hydrogen chloride (0.1 M; 20 ml). The aqueous phase was extracted with dichloromethane (3 × 20 ml). The combined organic phases were dried and evaporated to give the crude product.

#### 20 General procedure 3

The respective phenol (1.0 mmol), 3*H*-imidazol-1-ium iodide (1.0 mmol) and triethylamine (1.0 mmol) in acetonitrile (3 ml) was heated at 50 °C overnight in a closed vial. The crude product was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate/ heptane) yielding the respective carbamate.

#### 25 General procedure 4

Carbonyldiimidazole (3.6 mmol) was suspended in THF (10ml) and the appropriate secondary amine (3.0 mmol) was added. The reaction mixture was refluxed for 24 to 72 hours until no traces of amine could be detected. The reaction mixture was cooled to room temperature

and the organic phase evaporated to give the crude product of high purity. The crude product was used without further purification.

#### General procedure 5

5 The crude imidazole carboxamide (3.0 mmol) was dissolved in acetonitrile (10 ml) and methyl iodide (12 mmol.) was added at room temperature. The reaction mixture was stirred for 24 to 48 hours before the organic phase was evaporated to give the crude product, which was used without further purification.

#### General procedure 6

The respective 1,2,4-(1H)-triazoles were prepared as described by Blaine (US 3308131).

10

The 1,2,3-(1H)-triazoles were carbamoylated using the following method:

The respective 1,2,4-(1H)-triazole (2.0 mmol) was dissolved in dimethylformamide (10 ml) in a glass screw cap vessel, 1,4-diazabicyclo[2.2.2]octane (DABCO) (5.0 mmol) was added together with the respective carbamoyl chloride (5.0 mmol) at room temperature. The reaction mixture was stirred for 16 hours, evaporated to dryness and ethyl acetate (20 ml) and aqueous citric acid (5%; 20 ml) was added. The phases were separated and the aqueous phase extracted with ethyl acetate (20 ml). The combined organic phases were dried and evaporated to give the crude product.

#### 20 General procedure 7

The aryl chloroformate was prepared from the corresponding phenol, trichloromethyl chloroformate and ethyldiisopropylamine in dichloromethane according to the procedure described by T. Konakahara, T. Ozaki, K. Sato and B. Gold, Synthesis, 1993 (1) 103 - 106, except that the crude reaction mixture was used without removal of ethyldiisopropylamine hydrochloride.

25 To a stirred, freshly prepared solution of the aryl chloroformate in dichloromethane (1 mmol in 3 ml) at -15 °C was added a solution of the substituted piperazine (1 mmol) in dichloromethane (1 mL). The mixture was stirred at 0 °C for 2 - 6 h. The solvent was removed in vacuo and the solid residue was triturated with diethyl ether (3 x 5 ml), then with a minute amount of water (½ - 2 ml) to remove the ethyldiisopropylamine hydrochloride, filtered and dried to give the hydrochloride of the respective piperazine-1-carboxylic acid aryl ester.

30

**General procedure 8**

To a solution of the *N*-hydroxyazole (1.0 mmol) and ethyldiisopropylamine (1.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was added the respective carbamoyl chloride (1.5 mmol) at room temperature. The reaction mixture was stirred for 16 hours, added CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and washed with aqueous citric acid (5%; 3x20 mL). The organic phase was separated, dried (MgSO<sub>4</sub>) and evaporated to give the crude product.

**General procedure 9**

A solution of the substituted piperazine in diethyl ether is added to a stirred solution of an equimolar amount of the aryl chloroformate (prepared from the corresponding phenol by conventional methods) in the same solvent at 0 °C. After completion of the addition, the mixture is stirred at 0 °C for 1 hour, then for 1 more hour at room temperature. The mixture is filtered, the filter cake rinsed with diethyl ether and dried to give the hydrochloride of the respective piperazine-1-carboxylic acid aryl ester.

**General procedure 10**

A disubstituted amine (1.0 eq) and diisopropylethylamine (1.5 eq) was added to a dried reaction flask under nitrogen. Dichloromethane or tetrahydrofuran was added to give a 0.5 mM concentration of the amine. The appropriate aryl chloroformate (1.0 eq) (prepared from the corresponding phenol by conventional methods) was dissolved in a minimum amount of dichloromethane or tetrahydrofuran and added drop by drop at room temperature. The reaction mixture was stirred overnight, citric acid (5%) was added, and the two phases separated. The aqueous phase was extracted twice with dichloromethane, the combined organic phases were dried with MgSO<sub>4</sub>, filtered and evaporated to give the crude product.

**General procedure 11**

An appropriate amine (1.0 eq.) was dissolved in dichloromethane (0.5 mM concentration of the amine) in a dried reaction flask under nitrogen. The appropriate aryl chloroformate (1.0 eq.) (prepared from the corresponding phenol by conventional methods) was dissolved in a minimum amount of dichloromethane and added drop by drop at room temperature. Heptane was added to give a 20% solution in dichloromethane and the crude product was isolated by filtration. The crude product was washed with a mixture of dichloromethane/heptane (5:1) and dried in vacuum.

**General procedure 12**

An appropriate amine (1.0 eq.) and diisopropylethylamine (1.0 eq.) was dissolved in tetrahydrofuran (0.5 mM concentration of the amine) in a dried reaction flask under nitrogen. The appropriate aryl chloroformate (1.0 eq.) (prepared from the corresponding phenol by conventional methods) was dissolved in a minimum amount of tetrahydrofuran and added drop by drop at room temperature. Acetic acid was added to the reaction mixture (pH 3-5) and the reaction mixture filtered. The organic phase was evaporated and the crude product subjected to preparative HPLC.

#### General procedure 13

4-(Methyl-phenyl-carbamoyloxy)-benzoic acid 2,5-dioxo-pyrrolidin-1-yl ester (1 eq.), diisopropylethylamine (1.5 eq.) was dissolved in tetrahydrofuran (50 mM of phenol). The reaction mixture was added to a mono or disubstituted amine. The reaction mixture was stirred at 50 °C for 16 hours. Citric acid (5%) and *tert*-butyl-methylether was added and the two phases separated. The organic phase was evaporated to give the crude product.

#### General procedure 14

The phenol (1.0 mmol) was dissolved in tetrahydrofuran (15 ml) in a glass screw cap vessel, 1,4-diazabicyclo[2.2.2]octane (DABCO) (2.0 mmol) was added together with the respective carbamoyl chloride (2.0 mmol) at room temperature. The reaction mixture was shaken for 16 hours. Acetic acid was added to the reaction mixture (pH 3-5) and the reaction mixture filtered. The organic phase was evaporated and the crude product subjected to preparative HPLC.

#### General procedure 15

A solution of the substituted piperazine in diethyl ether was added to a stirred solution of an equimolar amount of the aryl chloroformate in the same solvent at 0 °C. After completion of the addition, the mixture was stirred at ambient temperature for 1 - 2 hours. Stirring was discontinued and as much as possible of the solvent was removed by decantation. The residue was rinsed twice with ether by stirring and subsequent decantation and finally dried on a rotary evaporator to give the hydrochloride of the respective piperazine-1-carboxylic acid aryl ester.

If necessary, further purification was achieved by treating the crude product with a mixture of ethyl acetate and a slight excess of sodium bicarbonate (approx. 1.1 eqv.) in water, extracting the aqueous phase twice with ethyl acetate, drying the combined extracts, filtering and evaporating to give the piperazine-1-carboxylic acid aryl ester as a free base.

**General procedure 16**

To a solution of the *N*-hydroxyazole (1.0 mmol) and ethyldiisopropylamine (1.0 mmol) in CHCl<sub>3</sub> (1 mL) at -30 °C was added trichloromethyl chloroformate (1.1 mmol). The solution was stirred at -30 °C for 10 min and at room temperature for 1 h. The solution was evaporated to dryness at room temperature and redissolved in CHCl<sub>3</sub> (2 mL) and cooled to -30 °C before addition of the appropriate piperazine (3 mmol). The solution was allowed to warm to room temperature over 30 min and evaporated to give the crude product.

**General procedure 17**

To a suspension of *N*-methyl-*N*-phenyl-carbamic acid 4-(2-amino-ethyl)phenyl ester as its TFA salt (0.5 mmol) and an aryl sulfonyl chloride (0.75 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added DIPEA (1.25 mmol). The reaction mixture was stirred at rt for 2-16 h, and evaporated to dryness and redissolved in MeCN and purified by preparative HPLC (Gilson).

**General procedure 18**

A solution of the substituted piperazine in diethyl ether was added to a stirred solution of an equimolar amount of the aryl chloroformate in the same solvent at 0 °C. Then an equimolar amount of diisopropylethylamine (DIPEA) in diethyl ether solution was added and the mixture was stirred at ambient temperature for 1 - 2 hours. The solvent was removed on a rotary evaporator and the residue was partitioned between ethyl acetate and water. The aqueous phase was extracted twice with ethyl acetate and the combined organic phases were dried and filtered. Removal of the solvent gave the piperazine-1-carboxylic acid aryl ester.

**General procedure 19**

4-Formyl-piperidine-1-carboxylic acid *tert*-butyl ester (1.5 g, 7.03 mmol) prepared as described by Ting, P. C. was added to a dried screw cap vessel under nitrogen. The appropriate amine (7.03 mmol) methanol (10 ml) and acetic acid 100 (μl) was added and the reaction mixture was stirred for 2 h. at room temperature. Sodium cyanoborohydride (1.0 M sol. In THF, 4.7 ml) was added during 1 minute and the mixture was stirred for 16 h. at room temperature. The reaction mixture was evaporated to dryness and extracted with dichloromethane (3 × 75 ml) from a 10 % aqueous sodium hydrogen carbonate solution (100 ml). The organic phases were pooled, dried, and evaporated to dryness to give the crude inter-

mediate, which was subjected to flash chromatography (ethyl acetate/heptane/methanol, 1:2:0 → 4:0:1).

A 3M solution of hydrogen chloride (50 ml) was added to the intermediate and the reaction mixture was stirred for 16 h. The reaction mixture was evaporated to dryness to give the crude product, which was dried in vacuum. The crude product was used without further purification.

#### General procedure 20

The arylboronic acid (1.2 mmol), KF (3.3 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (0.03 mmol) and Pd(P(*t*-Bu)<sub>3</sub>)<sub>2</sub> (0.06 mmol) were added to a Schlenk tube under nitrogen. The Schlenk tube was evacuated and refilled with nitrogen five times. Next the aryl halide (1.0 mmol) in THF (2 mL) was added. The reaction mixture was stirred at rt for 16 h.

#### General procedure 21

To a suspension of methyl-phenyl-carbamate 4-amino-phenyl ester (0.5 mmol), (see preparation below) and an aryl sulfonyl chloride (0.75 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added DIPEA (1.25 mmol). The reaction mixture was stirred at rt for 2-16 h, and evaporated to dryness and redissolved in MeCN and purified by preparative HPLC (Gilson).

#### General procedure 22

A solution of 1-benzyloxy-4-iodobenzene (4.1 mmol) in dry THF (20 mL) was cooled to -78 °C. *n*-Butyllithium (1.57 M in hexanes, 4.1 mmol) was added during 2 min. After the mixture was stirred for another 5 min, an aryl aldehyde (4.1 mmol) was added. The mixture was allowed to warm to rt during 20 min and quenched with aqueous NaHCO<sub>3</sub>. Extraction with CH<sub>2</sub>Cl<sub>2</sub>, drying (MgSO<sub>4</sub>), filtration and evaporation provided the crude diarylmethanols which were recrystallised from EtOAc-heptane. A solution of the diarylmethanol product (2 mmol), NaI (14 mmol) in dry MeCN (20 mL) was added trimethylsilyl chloride (14 mmol) and stirred at 80 °C for 19 h. The purple reaction mixture was evaporated to dryness and treated with an aqueous solution of Na<sub>2</sub>SO<sub>3</sub>. The 4-arylmethylphenols were isolated by filtration or after extraction with CH<sub>2</sub>Cl<sub>2</sub> and subsequent purification by flash chromatography (Quad flash 12, EtOAc-heptane).

**General procedure 23**

A solution of the sulfonamide (0.2 mmol), 37% aqueous formaldehyde (0.5 mL), and TFA (2 mL) was heated in a closed vessel in a Smith Creator microwave oven for 300 s at 150 °C. The crude product was evaporated to dryness and purified by preparative HPLC (Gilson).

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**General procedure 24**

A suspension of the phenol (1.0 mmol), 1,4-diazabicyclo[2.2.2]octane (DABCO) (1.5 mmol) and 3-[4-(tert-butyl-dimethyl-silyloxy)-piperidine-1-carbonyl]-1-methyl-3H-imidazol-1-ium; iodide (1.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was stirred at room temperature for 16 hours. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane). The purified tert-butyl dimethylsilyl ether was desilylated by stirring with a 3.2 M solution of HCl in Et<sub>2</sub>O (20 mL) for 3 h at rt.

10

**General procedure 25**

A solution of an alcohol (0.4 mmol), a phenol (0.4 mmol), diisopropylethylamin (0.44 mmol) and tributylphosphine (0.5 mmol) in THF (2 mL) was stirred under nitrogen at rt. ADDP (0.5 mmol) dissolved in THF (2 mL) was added and the reaction mixture was stirred at rt for 16 h, filtered, evaporated to dryness and redissolved in MeCN and purified by preparative HPLC (Gilson).

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**General procedure 26**

A solution of an alcohol (0.4 mmol), a phenol/thiophenol/N-hydroxyazole/azole or imide (0.4 mmol), diisopropylethylamin (0.44 mmol) and solid supported triphenylphosphine (3 mmol/g, 1.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was stirred under nitrogen at rt. Di-tert-butylazodicarboxylate (DBAD, 1.2 mmol) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was added and the reaction mixture was stirred at rt for 16 h. TFA (0.5 mL) was added and the mixture was stirred for further 1 h at rt. Addition of EtOAc, filtration, followed by evaporation to dryness gave a crude which was either purified by flash chromatography (Quad flash 12, EtOAc-heptane) or redissolved in MeCN and purified by preparative HPLC (Gilson).

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**Preparation of 1-methyl-3H-imidazol-1-ium iodides****1-Methyl-3-(7-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carbonyl)-3H-imidazol-1-ium iodide****5    Step A: Imidazol-1-yl-(7-trifluoromethyl-3,4-dihydro-2H-quinolin-1-yl)-methanone**

The title product was prepared from 7-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline, as described in the general procedure 4. Light yellow oil. HPLC-MS:  $m/z$  = 296.1 (M+1); Rt: 2.85 min.

10     $\delta_H$ (300MHz;  $CDCl_3$ ): 2.11 (qi, 2H), 2.93 (t, 2H), 3.90 (t, 2H), 7.01 (s, 2H), 7.05 (s, 1H), 7.34 (s, 1H), 7.34 (d, 1H), 7.77 (s, 1H).

**Step B: 1-Methyl-3-(7-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carbonyl)-3H-imidazol-1-ium iodide**

15    The title product was prepared from imidazol-1-yl-(7-trifluoromethyl-3,4-dihydro-2H-quinolin-1-yl)-methanone, as described in the general procedure 5. Light yellow crystals. HPLC-MS:  $m/z$  = 310.2 (M+1), Rt: 1.84 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 2.01 (qi, 2H), 2.94 (t, 2H), 3.83 (t, 2H), 3.92 (s, 3H), 7.52 (s, 2H), 7.76 (s, 1H), 7.80 (s, 1H), 7.85 (s, 1H), 9.62 (s, 1H).

20

**3-(cyclohexyl-methyl-carbamoyl)-1-methyl-3H-imidazol-1-ium iodide****Step A: Imidazole-1-carboxylic acid cyclohexyl-methyl-amide**

25    The title product was prepared from cyclohexyl-methyl-amine, as described in the general procedure 4. Off-white crystals. HPLC-MS:  $m/z$  = 208.1 (M+1), Rt: 1.85 min

$\delta_H$ (300MHz;  $CDCl_3$ ): 1.05-1.22 (m, 1H), 1.25-1.45 m, 2H), 1.50-1.61 (dt, 2H), 1.63-1.75 (d, 1H), 1.76-1.95 (m, 4H), 3.80-3.95 (m, 1H), 7.09 (bs, 1H), 7.21 (bs 1H), 7.87 (bs, 1H).

**Step B: 3-(cyclohexyl-methyl-carbamoyl)-1-methyl-3H-imidazol-1-ium iodide**



The title product was prepared from imidazole-1-carboxylic acid cyclohexyl-methyl-amide, as described in the general procedure 5. Yellow crystals; HPLC-MS:  $m/z = 222.2$  ( $M+1$ ), Rt: 1.15 min.

5  $\delta_H$ (300MHz;  $CDCl_3$ ): 1.03-1.25, (m, 1H), 1.30-1.60 (m, 4H), 1.62-1.1.78 (m, 1H), 1.82-2.00 (t, 4H), 3.21 (s, 3H), 3.90-4.10 (m, 1H), 4.29 (s, 3H), 7.52 (bs, 1H), 7.66 (bs, 1H), 10.37 (bs, 1H).

### 3-(2,6-dimethyl-morpholine-4-carbonyl)-1-methyl-3H-imidazol-1-ium iodide

#### 10 Step A: (2,6-Dimethyl-morpholin-4-yl)-imidazol-1-yl-methanone

The title product was prepared from 2,6-dimethyl-morpholine, as described in the general procedure 4. Colourless oil. PPLC-MS:  $m/z = 210.10$  ( $M+1$ ), Rt: 0.63 min.

15  $\delta_H$ (300MHz;  $CDCl_3$ ): 1.20 (s, 3H), 1.22 (s, 3H), 2.82 (dd, 2H), 3.60-3.75 (m, 2H), 3.93 (d, 2H), 7.11 (s, 1H), 7.20 (s, 1H), 7.87 (s, 1H).

#### Step B: 3-(2,6-dimethyl-morpholine-4-carbonyl)-1-methyl-3h-imidazol-1-ium iodide

The title product was prepared from, (2,6-Dimethyl-morpholin-4-yl)-imidazol-1-yl-methanone, as described in the general procedure 5. Light yellow oil; HPLC-MS:  $m/z = 224.2$  ( $M+1$ ), Rt: 20 0.40 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 1.23 (s, 3H), 1.25 (s, 3H), 2.90-3.10 (m, 2H), 3.7-3.9 (m, 2H), 3.95-4.15 (m, 2H), 4.26 (s, 3H), 7.67 (s, 1H), 7.73 (s, 1H)10.05 (s, 1H).

### 3-(Benzyl-methyl-carbamoyl)-1-methyl-3H-imidazol-1-ium iodide

#### 25 Step A: Imidazole-1-carboxylic acid benzyl-methyl-amide

The title product was prepared from benzyl-methyl-amine, as described in the general procedure 4. Light yellow crystals. HPLC-MS:  $m/z = 216.1$  ( $M+1$ ), Rt: 1.53 min.

30  $\delta_H$ (300MHz;  $CDCl_3$ ): 3.04 (s, 3H), 4.65 (s, 3H), 7.08 (bs, 1H), 7.22-7.34 (m, 3H), 7.34-7.50 (m, 3H), 7.93 (bs, bs, 1H).

**Step B: 3-(Benzyl-methyl-carbamoyl)-1-methyl-3H-imidazol-1-ium iodide**

The title product was prepared from imidazole-1-carboxylic acid benzyl-methyl-amide, as described in the general procedure 5. Light yellow crystals. HPLC-MS m/z = 230.1 (M+1), Rt:

5 1.23 min.

$\delta_H$ (300MHz; CDCl<sub>3</sub>): 3.25 (s, 3H), 4.2 (s, 3H), 4.76 (s, 2H), 7.27-7.50 (m, 5H), 7.56 (bs, 1H), 7.70 (bs, 1H), 10.29 (bs, 1H).

**3-(Phenyl-ethyl-carbamoyl)-1-methyl-3H-imidazol-1-ium iodide**

10

**Step A: Imidazole-1-carboxylic acid phenyl-ethyl-amide**

The title product was prepared from phenyl-ethyl-amine, as described in the general procedure 4. Light brown oil. HPLC-MS m/z = 216.1 (M+1), Rt: 1.75 min.

15  $\delta_H$ (300MHz; CDCl<sub>3</sub>): 1.26 (t, 3H), 3.92 (q, 2H), 6.79 (s, 1H), 6.84 (s, 1H), 7.10 (d, 2H), 7.27-7.45 (m, 3H), 7.55 (s, 1H).

**Step B: 3-(Phenyl-ethyl-carbamoyl)-1-methyl-3H-imidazol-1-ium iodide**

The title product was prepared from imidazole-1-carboxylic acid phenyl-ethyl-amide, as described in the general procedure 5. Light yellow crystals. HPLC-MS m/z = 230.2 (M+1), Rt:

20 1.16 min.

$\delta_H$ (300MHz; CDCl<sub>3</sub>): 1.28 (t, 3H), 3.96 (q, 2H), 4.10 (s, 3H), 7.03 (s, 1H), 7.27 (s, 1H), 7.35-7.60 (m, 6 H), 9.70 (s, 1H).

**3-(2,3-Dihydro-indole-1-carbonyl)-1-methyl-3H-imidazol-1-ium iodide**

25

**Step A: (2,3-Dihydro-indol-1-yl)-imidazol-1-yl-methanone**

The title product was prepared from indoline, as described in the general procedure 4. Pink crystals. HPLC-MS m/z = 214.1 (M+1), Rt: 1.62 min.

$\delta_H$ (300MHz; CDCl<sub>3</sub>): 3.21 (t, 2H), 4.21 (t, 2H), 7.21 (dt, 1H), 7.15 (s, 1H), 7.17-7.29 (m, 2H), 7.36 (t, 1H), 7.40 (d, 1H), 8.03 (bs, 1H).

**Step B:** 3-(2,3-Dihydro-indole-1-carbonyl)-1-methyl-3H-imidazol-1-ium iodide

- 5 The title product was prepared from (2,3-dihydro-indol-1-yl)-imidazol-1-yl-methanone, as described in the general procedure 5. Light brown crystals. HPLC-MS m/z = 228.1 (M+1), Rt: 0.94 min.

$\delta_H$ (300MHz; CDCl<sub>3</sub>): 3.42 (t, 2H), 4.34 (s, 3H), 4.71 (t, 2H), 7.17-7.36 (m, 4H), 7.78 (bs, 1H), 7.86 (d, 1H), 10.76 (bs, 1H).

10

**3[(4-Chlorophenyl)-methyl-carbamoyl]-1-methyl-3H-imidazol-1-ium iodide**

**Step A:** Imidazole-1-carboxylic acid (4-chloro-phenyl)-methyl-amide

- 15 The title product was prepared from 4-chlor-N-methylaniline, as described in the general procedure 4. Light yellow crystals. HPLC-MS m/z = 236.1 g/mol (M+1), Rt: 1.91 min.

$\delta_H$ (300MHz; CDCl<sub>3</sub>): 3.47 (s, 3H), 6.85 (s, 1H), 6.87 (s, 1H), 7.06 (d, 2H), 7.36 (d, 2H), 7.60 (s, 1H).

**Step B:** [(4-Chlorophenyl)-methyl-carbamoyl]-1-methyl-3H-imidazol-1-ium iodide

- 20 The title product was prepared from imidazole-1-carboxylic acid (4-chloro-phenyl)-methyl-amide, as described in the general procedure 5. Orange crystals. HPLC-MS m/z = 250.1 (M+1), Rt: 1.06 min.

$\delta_H$ (300MHz; CDCl<sub>3</sub>): 3.55 (s, 3H), 4.12 (s, 3H), 7.16 (bs, 1H), 7.35 (t, 1H), 7.41 (d, 1H), 7.45 (t, 1H), 7.51 (t, 1H), 7.53-7.55 (m, 1H), 9.92 (bs, 1H).

25

**3-(isopropyl-methyl-carbamoyl)-1-methyl-3H-imidazol-1-ium iodide**

**Step A:** Imidazole-1-carboxylic acid isopropyl-methyl-amide

The title product was prepared from isopropyl-methylamine, as described in the general procedure 4. Light yellow oil. HPLC-MS  $m/z$  = 168.1 ( $M+1$ ),  $R_t$ : 0.51 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 1.25 (s, 3H), 1.27 (s, 3H), 2.93 (s, 3H), 4.36 (q, 1H), 7.08 (bs, 1H), 7.22 (bs, 1H), 7.88 (bs, 1H).

5 Step B: 3-(isopropyl-methyl-carbamoyl)-1-methyl-3H-imidazol-1-ium iodide

The title product was prepared from imidazole-1-carboxylic acid isopropyl-methyl-amide, as described in the general procedure 5. Light yellow crystals. HPLC-MS  $m/z$  = 182.2 ( $M+1$ ),  $R_t$ : 0.41 min.

10  $\delta_H$ (300MHz;  $CDCl_3$ ): 1.31 (s, 3H), 1.35 (s, 3H), 3.17 (s, 3H), 4.29 (s, 3H), 4.30-4.50 (m, 2H), 7.62 bs, 1H), 7.71 (bs, 1H), 10.29 (bs, 1H).

**3-(1,3-Dihydroisoindole-2-carbonyl)-1-methyl-3H-imidazol-1-ium iodide**

Step A: (1,3-Dihydroisoindole-1-yl)-imidazol-1-yl-methanone

15

The title product was prepared from isoindole, as described in the general procedure 4. Oil.

Step B: 3-(1,3-Dihydroisoindole-2-carbonyl)-1-methyl-3H-imidazol-1-ium iodide

20 The title product was prepared from (1,3-dihydroisoindole-1-yl)-imidazol-1-yl-methanone, as described in the general procedure 5. Crystals.

$\delta_H$ (300MHz;  $CDCl_3$ ): 3.96 (s, 3H), 4.98 (s, 2H), 5.04 (s, 2H), 7.35 (bs, 3H), 7.44 (bs, 1H), 7.91 (s, 1H), 8.21 (s, 1H), 9.74 (s, 1H).

**1-Methyl-3-(piperidine-1-carbonyl)-3H-imidazol-1-ium iodide**

25 Step A: Piperidin-1-yl-imidazol-1-yl-methanone

The title product was prepared from piperidine, as described in the general procedure 4. Oil.

Step B: 1-Methyl-3-(piperidine-1-carbonyl)-3H-imidazol-1-ium iodide

The title product was prepared from piperidin-1-yl-imidazol-1-yl-methanone, as described in the general procedure 5. Oil.

$\delta_H$ (300MHz; CDCl<sub>3</sub>): 1.74 (s, 6H), 3.66 (bs, 4H), 4.28 (s, 3H), 7.78 (s, 1H), 7.83 (s, 1H), 10.07 (s, 1H).

### **1-Methyl-3-(2-methyl-piperidine-1-carbonyl)-3H-imidazol-1-ium iodide**

#### Step A: (2-Methyl-piperidin-1-yl)-imidazol-1-yl-methanone

The title product was prepared from 2-methyl-piperidine, as described in the general procedure 4. light yellow oil. HPLC-MS m/z = 194.2 (M+1), Rt: 0.92 min.

$\delta_H$ (300MHz; CDCl<sub>3</sub>): 1.33 (d, 3H) 1.45-1.67 (m, 2H), 1.68-1.85 (m, 4H), 3.17 (dt, 1H), 3.86 (dd, 1H), 4.35-4.50 (m, 1H), 7.09 (s, 1H), 7.18 (s, 1H), 7.84 (s, 1H).

#### Step B: 1-Methyl-3-(2-methyl-piperidine-1-carbonyl)-3H-imidazol-1-ium iodide

15

The title product was prepared from (2-methyl-piperidin-1-yl)-imidazol-1-yl-methanone, as described in the general procedure 5. Orange solid. HPLC-MS m/z = 208.1 (M+1), Rt: 0.57min.

$\delta_H$ (300MHz; CDCl<sub>3</sub>): 1.40 (d, H), 1.60-1.98 m, 6H), 3.45 (t, 1H), 3.90 (d, 1H), 4.30 (s, 3H), 4.45-4.60 (m, 1H), 7.59 (s, 1H), 7.62 (s, 1H), 10.06 (s, 1H).

### **1-Methyl-3-(3-methyl-piperidine-1-carbonyl)-3H-imidazol-1-ium iodide**

#### Step A: (3-Methyl-piperidin-1-yl)-imidazol-1-yl-methanone

The title product was prepared from 3-methyl-piperidine, as described in the general procedure 4. light yellow oil. HPLC-MS m/z = 194.2 (M+1), Rt: 1.15 min.

$\delta_H$ (300MHz; CDCl<sub>3</sub>): 0.94 (d, 3H), 1.05-1.35 (m, 1H), 1.50-2.00 (m, 4H), 2.67 (t, 1H), 3.01 (dt, 1H), 3.98 (t, 2H), 7.09 (s, 1H), 7.19 (s, 1H), 7.85 (s, 1H).

#### Step B: 1-Methyl-3-(3-methyl-piperidine-1-carbonyl)-3H-imidazol-1-ium iodide

The title product was prepared from (3-methyl-piperidin-1-yl)-imidazol-1-yl-methanone, as described in the general procedure 5. Yellow oil. HPLC-MS  $m/z$  = 208.1 ( $M+1$ ), Rt: 0.69min.  $\delta_H$ (300MHz;  $CDCl_3$ ): 0.97 (d, 3H), 1.15-1.40 (m, 1H), 1.55-2.00 (m, 4H), 2.92 (t, 1H), 3.28 (t, 1H), 3.90-4.15 (m, 2H), 4.28 (s, 3H), 7.60-7.75 (m, 2H), 10.14 (s, 1H).

1-Methyl-3-(4-methyl-piperidine-1-carbonyl)-3H-imidazol-1-ium iodide

Step A: (4-Methyl-piperidin-1-yl)-imidazol-1-yl-methanone

The title product was prepared from 4-methyl-piperidine, as described in the general procedure 4. light yellow oil. HPLC-MS  $m/z$  = 194.2 ( $M+1$ ), Rt: 1.32 min.  $\delta_H$ (300MHz;  $CDCl_3$ ): 1.00 (d, 3H), 1.15-1.35 (m, 2H), 1.55-1.85 (m, 3H), 3.02 (dt, 2H), 4.08 (d, 2H), 7.08 (s, 1H), 7.19 (s, 1H), 7.85 (s, 1H).

Step B: 1-Methyl-3-(4-methyl-piperidine-1-carbonyl)-3H-imidazol-1-ium iodide

The title product was prepared from (4-methyl-piperidin-1-yl)-imidazol-1-yl-methanone, as described in the general procedure 5. Yellow oil. HPLC-MS  $m/z$  = 208.1 ( $M+1$ ), Rt: 0.65min.  $\delta_H$ (300MHz;  $CDCl_3$ ): 1.00 (d, 3H), 1.20-1.50 (m, 2H), 1.66-1.90 (m, 3H), 3.32 (t, 2H), 4.13 (d, 2H), 4.28 (s, 3H), 7.58 (s, 1H), 7.64 (s, 1H), 10.15 (s, 1H).

1-Methyl-3-(4-benzyl-piperidine-1-carbonyl)-3H-imidazol-1-ium iodide

Step A: (4-Benzyl-piperidin-1-yl)-imidazol-1-yl-methanone

The title product was prepared from 4-methyl-piperidine, as described in the general procedure 4. light yellow oil. HPLC-MS  $m/z$  = 270.2 ( $M+1$ ), Rt: 2.58 min.  $\delta_H$ (300MHz;  $CDCl_3$ ): 1.10-1.50 (m, 2H), 1.65-2.00 (m, 3H), 2.59 (d, 2H), 2.97 (dt, 2H), 4.08 (d, 2H), 7.05-7.40 (m, 7H), 7.84 (s, 1H).

Step B: 1-Methyl-3-(4-benzyl-piperidine-1-carbonyl)-3H-imidazol-1-ium iodide

The title product was prepared from (4-benzyl-piperidin-1-yl)-imidazol-1-yl-methanone, as described in the general procedure 5. Yellow oil. HPLC-MS  $m/z$  = 208.1 ( $M+1$ ), Rt: 0.65min.

$\delta_{\text{H}}$ (300MHz;  $\text{CDCl}_3$ ): 1.30-1.50 (m, 2H), 1.75-1.95 (m, 3H), 2.59 (d, 2H), 3.15-3.40 (m, 2H), 4.05-4.20 (m, 2H), 4.25 (s, 3H), 7.10-7.35 (m, 5H), 7.45 (bs, 1H), 7.60 (bs, 1H), 10.22 (s, 1H).

5 **1-Methyl-3-(1,2,3,4-tetrahydroisoquinoline-1-carbonyl)-3H-imidazol-1-ium iodide**

Step A: (1,2,3,4-Tetrahydroisoquinoline-1-yl)-imidazol-1-yl-methanone

The title product was prepared from 1,2,3,4-tetrahydroisoquinoline, as described in the general procedure 4. Oil.

10 Step B: 1-Methyl-3-(1,2,3,4-tetrahydroisoquinoline-1-carbonyl)-3H-imidazol-1-ium iodide

The title product was prepared from (1,2,3,4-tetrahydroisoquinoline-1-yl)-imidazol-1-yl-methanone, as described in the general procedure 5. Oil.

15  $\delta_{\text{H}}$ (300MHz;  $\text{CDCl}_3$ ): 2.97 (t, 2H), 3.73 (bs, 2H), 3.94 (s, 3H), 4.75 (s, 2H), 7.15-7.35 (m, 4H), 7.88 (d, 1H), 8.09 (d, 1H), 9.63 (s, 1H).

**Preparation of Phenols**

20 **1-(4-Hydroxy-phenyl)-4,4-dimethyl-piperidine-2,6-dione**

A mixture of 4-aminophenol (3.27 g, 30.0 mmol) and 3,3-dimethylglutaric anhydride (4.26 g, 30.0 mmol) was heated in a round bottom flask at 165 °C for 1 h, followed by heating at 180 °C for 7 h. After cooling to room temperature the solid material was dissolved in hot ethanol,  
25 activated charcoal was added and the solution was heated at reflux for 1 h. The solid material was removed by hot filtration. The solvent was evaporated and the residue was crystallised from water/ethanol yielding the title compound (3.51 g, 50% yield, pink solid).

$^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  1.08 (s, 6H), 2.63 (s, 4H), 6.77 + 6.86 (AB-system, 4H), 9.56 (s, 1H).

***cis*-2-(4-Hydroxy-phenyl)-hexahydro-isoindole-1,3-dione**

A mixture of 4-aminophenol (5.46 g, 50.0 mmol) and *cis*-1,2-cyclohexanedicarboxylic anhydride (7.71 g, 50.0 mmol) was heated in a round bottom flask at 170 °C for 2 h. After cooling to room temperature the solid material was dissolved in hot ethanol (200 ml), activated charcoal was added and the solution was heated at reflux for 1 h. The solid material was removed by hot filtration. The solvent was partially evaporated. The solids were collected by filtration, washed quickly with a small amount of ethanol and dried *in vacuo* at 40 °C yielding the title compound (8.52 g, 69% yield, pink solid).

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 1.38 (m, 4H), 1.73 (m, 4H), 3.02 (m, 2H), 6.82 (d, 2H), 7.02 (d, 2H), 9.66 (s, 1H, OH); HPLC-MS: *m/z* = 246 (M+1); *R*<sub>t</sub> = 2.53 min.

**Cyclohexanecarboxylic acid (4-hydroxy-phenyl)-amide**

15

To a solution of 4-aminophenol (5.00 g, 45.8 mmol) in dichloromethane (50 ml) were added cyclohexanecarbonyl chloride (6.72 g, 45.8 mmol) and pyridine (3.70 ml, 45.8 mmol), while cooling the reaction mixture in an ice bath. After the addition was completed, the cooling bath was removed and stirring was continued overnight at room temperature. Water (100 ml) was added, the organic phase was removed and the resulting solution was extracted with ethyl acetate (3 x 300 ml). The combined organic phases were washed with water (2 x 200 ml), dried, filtered and evaporated, yielding an off-white solid. The crude product was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate/heptane (40:60)), yielding a mixture of two compounds, which were dissolved in THF. 6N NaOH (aq, 32 ml) was added and the mixture was stirred at room temperature for 2.5 h. The solution was acidified with concentrated hydrochloric acid and the organic solvent was removed by evaporation. The solid material was collected by filtration, dried and recrystallised from ethyl acetate/heptane, yielding the title compound (4.20 g, 41%, off-white solid).

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 1.12-1.48 (m, 5H), 1.65 (m, 1H), 1.70-1.82 (m, 4H), 2.27 (m, 1H), 6.66 (d, 2H), 7.36 (d, 2H), 9.10 (s, 1H), 9.50 (s, 1H); HPLC-MS: *m/z* = 220 (M+1); *R*<sub>t</sub> = 2.69 min.



**2-Cyclohexyl-N-(4-hydroxy-phenyl)-acetamide**

To a solution of 4-aminophenol (3.83 g, 35.1 mmol) in dichloromethane (50 ml) were added  
5 cyclohexylacetyl chloride (11.26 g, 70.1 mmol) and pyridine (5.67 ml, 70.1 mmol), while cool-  
ing the reaction mixture in an ice bath. After the addition was completed, the cooling bath  
was removed and stirring was continued overnight at room temperature. The solvent was  
removed and the residue was dissolved in THF (300 ml). 6N NaOH (aq, 41 ml) was added  
and the mixture was stirred at room temperature for 4 h. The solution was acidified with 1 N  
10 hydrochloric acid. The solvent was removed by evaporation. The solid material was collected  
by filtration, dried *in vacuo* at 40 °C and dissolved in methanol (100 ml). A solution of KOH  
(5.5 g) in methanol (50 ml) was added. After stirring for 1 h at room temperature water (200  
ml) was added and the organic solvent was removed by evaporation. The aqueous phase  
was acidified with 1 N HCl. The solid material was isolated by filtration and dried *in vacuo* at  
15 40 °C yielding the title compound (6.31 g, 77% yield, pink crystals).

<sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 0.82-1.32 (m, 5H), 1.54-1.76 (m, 6H), 2.12 (d, 2H), 6.66 (d, 2H), 7.32 (d, 2H), 9.12 (s, 1H), 9.57 (s, 1H); HPLC-MS: *m/z* = 234 (M+1); R<sub>t</sub> = 3.09 min.

***cis/trans*-4-tert-Butyl-cyclohexanecarboxylic acid (4-hydroxy-phenyl)-amide**

20

To a solution of 4-aminophenol (3.08 g, 28.2 mmol) in dichloromethane (50 ml) were added  
*cis/trans*-4-tert-butyl-cyclohexanecarbonyl chloride (11.43 g, 56.4 mmol) and pyridine (4.56  
ml, 56.4 mmol), while cooling the reaction mixture in an ice bath. After the addition was com-  
pleted, the cooling bath was removed and stirring was continued overnight at room tempera-  
25 ture. The solvent was removed by evaporation and the residue was dissolved in THF (300  
ml). 6N NaOH (aq, 33 ml) was added and the mixture was stirred at room temperature over-  
night. The organic phase was removed by evaporation. Water (200 ml) was added and the  
solid material was collected by filtration, washed with water, dried *in vacuo* at 40 °C and dis-  
solved in methanol (100 ml). A solution of KOH (2.4 g) in methanol (50 ml) was added. After  
30 stirring for 2 h at room temperature water (200 ml) was added and the organic phase was  
removed by evaporation. The aqueous phase was acidified with 1 N HCl and extracted with

ethyl acetate (3 x 300 ml). The combined organic phases were washed with saturated sodium bicarbonate, dried, filtered and evaporated, yielding a pink oil, which was dried *in vacuo* at 40 °C. The solid material was crystallised from ethyl acetate/heptane yielding the title compound (2.03 g, 26%, pink crystals). From the first aqueous extract a second portion of product was isolated by extraction with ethyl acetate (3 x 250 ml). The combined organic phases were washed with water (400 ml), saturated sodium bicarbonate (2 x 400 ml), dried, filtered and evaporated, yielding a pink thick oil. Crystallisation from ethyl acetate/heptane yielded a further amount of title compound (2.75 g, 35%).

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 0.80 + 0.84 (2 x s, 9H), 0.98 (m, 2H), 1.23-1.57 (m, 4H), 1.76-1.90 (m, 2H), 2.02-2.14 (m, 1.5H), 2.57 (m, 0.5H), 6.65 (d, 2H), 7.34 (d x d, 2H), 9.09 (s, 1H), 9.36 + 9.50 (2 x s, 1H); HPLC-MS: *m/z* = 276 (M+1); *R*<sub>t</sub> = 4.19 and 4.27 min.

#### ***N*-(4-Hydroxy-phenyl)-3,3-dimethyl-butyramide**

15 To a solution of 4-aminophenol (3.27 g, 30.0 mmol) in dichloromethane (50 ml) were added 3,3-dimethyl-butyryl chloride (8.08 g, 60.0 mmol) and pyridine (4.85 ml, 60.0 mmol), while cooling the reaction mixture in an ice bath. After the addition was completed, the cooling bath was removed and stirring was continued overnight at room temperature. The solvent was removed by evaporation and the residue was dissolved in THF (300 ml). 6N NaOH (aq, 35 ml) was added and the mixture was stirred at room temperature overnight. The organic phase was removed by evaporation. Water (200 ml) was added and the solid material was collected by filtration, washed with water, dried *in vacuo* at 40 °C and dissolved in methanol (100 ml). A solution of KOH (3.37 g) in methanol (50 ml) was added. After stirring for 2 days at room temperature water (300 ml) was added and the organic solvent was removed by evaporation. The aqueous phase was acidified with 1 N HCl. The solids were collected by filtration and dried under vacuum at 40 °C yielding the title compound (1.97 g, 31%, pink solid). The mother liquor was extracted with ethyl acetate (3 x 250 ml). The combined organic phases were washed with saturated sodium bicarbonate (2 x 250 ml), dried *in vacuo*, filtered and evaporated yielding a second amount of the title compound (0.67 g, 10%). From the first aqueous extract another portion of product was isolated by extraction with ethyl acetate (4 x 250 ml). The combined organic phases were washed with water (400 ml), saturated sodium bicarbonate (2 x 400 ml), dried, filtered and evaporated yielding a pink thick oil. Cryst-

tallisation from ethyl acetate/heptane yielded a third amount of the title compound (2.11 g, 34%).

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  1.00 (s, 9H), 2.12 (s, 2H), 6.67 (d, 2H), 7.33 (d, 2H), 9.12 (s, 1H), 9.50 (s, 1H); HPLC-MS: *m/z* = 208 (M+1); *R*<sub>t</sub> = 2.50 min.

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#### **1-(4-Hydroxy-phenyl)-4,4-dimethyl-piperidine-2,6-dione**

A mixture of 4-aminophenol (3.27 g, 30.0 mmol) and 3,3-dimethylglutaric anhydride (4.26 g, 30.0 mmol) was heated in a round bottom flask at 165 °C for 1 h, followed by heating at 180 °C for 7 h. After cooling to room temperature the solid material was dissolved in hot ethanol, activated charcoal was added and the solution was heated at reflux for 1 h. The solid material was removed by hot filtration. The solvent was evaporated and the residue was crystallised (water/ethanol) yielding the title compound (3.51 g, 50%, pink solid).

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  1.08 (s, 6H), 2.63 (s, 4H), 6.77 + 6.86 (AB-system, 4H), 9.56 (s, 1H).

#### ***cis*-2-(4-Hydroxy-phenyl)-hexahydro-isoindole-1,3-dione**

A mixture of 4-aminophenol (5.46 g, 50.0 mmol) and *cis*-1,2-cyclohexanedicarboxylic anhydride (7.71 g, 50.0 mmol) was heated in a round bottom flask at 170 °C for 2 h. After cooling to room temperature the solid material was dissolved in hot ethanol (200 ml), activated charcoal was added and the solution was heated at reflux for 1 h. The solid material was removed by hot filtration. The solvent was partially evaporated. The solids were collected by filtration, washed quickly with a small amount of ethanol and dried *in vacuo* yielding the title compound (8.52 g, 69%, pink solid).

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  1.38 (m, 4H), 1.73 (m, 4H), 3.02 (m, 2H), 6.82 (d, 2H), 7.02 (d, 2H), 9.66 (s, 1H, OH); HPLC-MS: *m/z* = 246 (M+1); *R*<sub>t</sub> = 2.53 min.

**Cyclohexanecarboxylic acid (4-hydroxy-phenyl)-amide**

To a solution of 4-aminophenol (5.00 g, 45.8 mmol) in dichloromethane (50 ml) were added  
5 cyclohexanecarbonyl chloride (6.72 g, 45.8 mmol) and pyridine (3.70 ml, 45.8 mmol), while  
cooling the reaction mixture in an ice bath. After the addition was completed, the cooling bath  
was removed and stirring was continued overnight at room temperature. Water (100 ml) was  
added, the dichloromethane was removed by evaporation and the resulting solution was ex-  
tracted with ethyl acetate (3 x 300 ml). The combined organic phases were washed with wa-  
10 ter (2 x 200 ml), dried, filtered and evaporated, yielding an off-white solid. The crude product  
was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate/heptane (2:3)), yielding a  
mixture of two compounds, which were dissolved in THF. 6N NaOH (aq, 32 ml) was added  
and the mixture was stirred at room temperature for 2.5 h. The solution was acidified with  
concentrated hydrochloric acid. The THF was removed by evaporation. The solid material  
15 was collected by filtration, dried *in vacuo* and recrystallised (ethyl acetate/heptane), yielding  
the title compound (4.20 g, 41%, off-white solid).

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  1.12-1.48 (m, 5H), 1.65 (m, 1H), 1.70-1.82 (m, 4H), 2.27  
(m, 1H), 6.66 (d, 2H), 7.36 (d, 2H), 9.10 (s, 1H), 9.50 (s, 1H); HPLC-MS: *m/z* = 220 (M+1); *R*<sub>t</sub>  
= 2.69 min.

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**2-Cyclohexyl-N-(4-hydroxy-phenyl)-acetamide**

To a solution of 4-aminophenol (3.83 g, 35.1 mmol) in dichloromethane (50 ml) were added  
cyclohexylacetyl chloride (11.26 g, 70.1 mmol) and pyridine (5.67 ml, 70.1 mmol), while cool-  
25 ing the reaction mixture in an ice bath. After the addition was completed, the cooling bath  
was removed and stirring was continued overnight at room temperature. The solvent was  
removed by evaporation and the residue was dissolved in THF (300 ml). 6N NaOH (aq, 41  
ml) was added and the mixture was stirred at room temperature for 4 h. The solution was  
acidified with 1 N hydrochloric acid and the organic phase was removed by evaporation. The  
30 solid material was collected by filtration, dried and dissolved in methanol (100 ml). A solution  
of KOH (5.5 g) in methanol (50 ml) was added. After stirring for 1 h at room temperature wa-  
ter (200 ml) was added and the organic solvent was removed by evaporation. The aqueous

phase was acidified with 1 N HCl. The title product was isolated by filtration and dried *in vacuo* (6.31 g, 77%, pink crystals).

$^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  0.82-1.32 (m, 5H), 1.54-1.76 (m, 6H), 2.12 (d, 2H), 6.66 (d, 2H), 7.32 (d, 2H), 9.12 (s, 1H), 9.57 (s, 1H); HPLC-MS:  $m/z$  = 234 (M+1);  $R_t$  = 3.09 min.

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***cis/trans*-4-tert-Butyl-cyclohexanecarboxylic acid (4-hydroxy-phenyl)-amide**

To a solution of 4-aminophenol (3.08 g, 28.2 mmol) in dichloromethane (50 ml) were added *cis/trans*-4-tert-butyl-cyclohexanecarbonyl chloride (11.43 g, 56.4 mmol) and pyridine (4.56  
10 ml, 56.4 mmol), while cooling the reaction mixture in an ice bath. After the addition was completed, the cooling bath was removed and stirring was continued overnight at room temperature. The solvent was removed by evaporation and the residue was dissolved in THF (300 ml). 6N NaOH (aq, 33 ml) was added and the mixture was stirred at room temperature overnight. The organic phase was removed by evaporation. Water (200 ml) was added and the  
15 solid material collected by filtration, washed with water, dried and dissolved in methanol (100 ml). A solution of KOH (2.4 g) in methanol (50 ml) was added. After stirring for 2 h at room temperature water (200 ml) was added and the organic solvent was removed by evaporation. The aqueous phase was acidified with 1 N HCl and extracted with ethyl acetate (3 x 300 ml). The combined organic phases were dried and evaporated, yielding a pink oil, which was  
20 dried *in vacuo*. The solid material was crystallised from ethyl acetate/heptane yielding the title compound (2.03 g, 26%) as pink crystals. From the first aqueous extract a second portion of product was isolated by extraction with ethyl acetate (3 x 250 ml). The combined organic layers were washed with water (400 ml), saturated sodium bicarbonate (2 x 400 ml), dried, filtered and evaporated, yielding a pink thick oil. Crystallisation from ethyl acetate/heptane yielded a second amount of the title compound (2.75 g, 35%).  
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$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  0.80 + 0.84 (2 x s, 9H), 0.98 (m, 2H), 1.23-1.57 (m, 4H), 1.76-1.90 (m, 2H), 2.02-2.14 (m, 1.5H), 2.57 (m, 0.5H), 6.65 (d, 2H), 7.34 (d x d, 2H), 9.09 (s, 1H), 9.36 + 9.50 (2 x s, 1H); HPLC-MS:  $m/z$  = 276 (M+1);  $R_t$  = 4.19 and 4.27 min.

30 ***N*-(4-Hydroxy-phenyl)-3,3-dimethyl-butyramide**

To a solution of 4-aminophenol (3.27 g, 30.0 mmol) in dichloromethane (50 ml) were added 3,3-dimethyl-butyryl chloride (8.08 g, 60.0 mmol) and pyridine (4.85 ml, 60.0 mmol), while cooling the reaction mixture in an ice bath. After the addition was completed, the cooling bath was removed and stirring was continued overnight at room temperature. The solvent was removed by evaporation and the residue was dissolved in THF (300 ml). 6N NaOH (aq, 35 ml) was added, the mixture was stirred at room temperature overnight and the solvent was removed by evaporation. Water (200 ml) was added and the solid material is collected by filtration, washed with water, dried *in vacuo* at 40 °C and dissolved in methanol (100 ml). A solution of KOH (3.37 g) in methanol (50 ml) was added. After stirring for 2 days at room temperature water (300 ml) was added, the organic solvent was removed and the aqueous phase was acidified with 1 N HCl. The solids were collected and dried yielding the title compound (1.97 g, 31% yield, pink solid). The mother liquor was extracted with ethyl acetate (3 x 250 ml). The combined organic phases were washed with saturated sodium bicarbonate (2 x 250 ml), dried over sodium sulphate, filtered and evaporated yielding a second amount of the title compound (0.67 g, 10%). From the first aqueous extract another portion of product was isolated by extraction with ethyl acetate (4 x 250 ml). The combined organic phases were washed with water (400 ml), dried, filtered and evaporated yielding a pink thick oil. Crystallisation from ethyl acetate/heptane yielded a third amount of the title compound (2.11 g, 34%). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 1.00 (s, 9H), 2.12 (s, 2H), 6.67 (d, 2H), 7.33 (d, 2H), 9.12 (s, 1H), 9.50 (s, 1H); HPLC-MS: *m/z* = 208 (M+1); R<sub>t</sub> = 2.50 min.

#### 4-(3-Trifluoromethyl-phenoxy)-phenol

Hydroquinone monobenzylether (1 g, 5.0 mmol), 3-(trifluoromethyl)-phenyl boronic acid (1.9 g, 10.0 mmol), copper (II) acetate (0.91 g, 5.0 mmol) and triethylamine (2.53 g, 25.0 mmol) were dissolved/suspended in dichloromethane (50 ml). The reaction mixture was stirred for 70 h. at room temperature and evaporated to dryness. The crude intermediate was subjected to flash chromatography (ethyl acetate/heptane (1:4)) (42%) and hydrogenated (10% Pd/C) using ethanol as a solvent. The organic phase was evaporated and aqueous sodium hydroxide (1N, 30 ml) was added together with dichloromethane. The two phases were separated and the aqueous phase extracted with dichloromethane (30 ml x 2). The aqueous phase was acidified with aqueous hydrochloric acid (2N) and extracted with dichloromethane (30 ml x 5). The organic phase was dried and evaporated to give the crude product (47%). HPLC-MS *m/z* = 254.9 (M+1), R<sub>t</sub>: 4.39 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 6.85 (dt, 2H), 6.94 (dt, 2H), 7.10 (dd, 1H), 7.16 (bs, 1H), 7.24-7.30 (m, 1H), 7.39 (t, 1H).

#### 4-Hydroxy-benzoic acid 2,5-dioxo-pyrrolidin-1-yl ester

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4-Hydroxybenzoic acid (30 g, 0.217 mmol) and 4-hydroxysuccinamide (25.32 g, 0.220mmol) were dissolved in 1,4-dioxane (550 ml) at room temperature. After 20 min. the clear solution was cooled to 15°C and dicyclohexylcarbodiimide (44.82 ml, 0.217 mmol) was added. The reaction mixture was stirred for 18 hours and filtered. The organic phase was evaporated to dryness (86 g). Ethanol (250 ml) was added to the crude product and the mixture heated to reflux. The crude product was crystallized from ethanol/water (5:1) (22 g, 43%), and the mother liquor recrystallized from ethanol/water (25 g, 49%). HPLC-MS:  $m/z$  = (M+1);  $R_t$ : min.

#### N-(6-Methoxy-pyridin-3-yl)-benzamide

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A solution of 5-amino-2-methoxypyridine (2.48 g, 20.0 mmol) and *N*-ethyldiisopropylamine (2.84 g, 22.0 mmol) in dichloromethane (20 ml) was cooled in an ice-bath. Benzoyl chloride (3.09 g, 22 mmol) was slowly added by means of a syringe. The cooling bath was removed and stirring was continued at room temperature for 18 hours. Dichloromethane was added and the solution was extracted with water. The organic layer was dried over sodium sulphate, filtered and evaporated *in vacuo* leaving a dark solid. Crystallisation from ethyl acetate:heptane yielded the title compound (3.44 g, 75% yield).

$^1H$  NMR (300MHz,  $CDCl_3$ ):  $\delta$  3.93 (s, 3H), 6.77 (d, 1H), 7.44-7.59 (m, 3H), 7.81 (br.s, 1H), 7.87 (d, 2H), 8.01 (dd, 1H), 8.16 (d, 1H); HPLC-MS (Method A):  $m/z$  = 229 (M+H);  $R_t$  = 2.52 min.

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#### Cyclohexanecarboxylic acid (6-methoxy-pyridin-3-yl)-amide hydrochloride

5-Amino-2-methoxypyridine (3.72 g, 30.0 mmol), dissolved in a small amount of tetrahydrofuran, was added slowly to a solution of cyclohexanecarbonyl chloride (4.40 g, 30.0 mmol) in tetrahydrofuran (25 ml). After standing for 0.5 hours diethyl ether (250 ml) was added and the solids were collected by suction yielding the title compound (8.12 g, 100% yield) as a purple solid.

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<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 1.11-1.48 (m, 5H), 1.63 (m, 1H), 1.68-1.83 (m, 4H), 2.32 (m, 1H), 3.81 (s, 3H), 6.80 (d, 1H), 7.92 (dd, 1H), 8.00 (br.s, 1H), 8.38 (d, 1H), 9.92 (s, 1H); HPLC-MS (Method A): *m/z* = 235 (M+H); *R<sub>t</sub>* = 2.89 min.

5 **6'-Methoxy-4,4-dimethyl-4,5-dihydro-3H-[1,3']bipyridinyl-2,6-dione**

A mixture of 5-amino-2-methoxypyridine (3.72 g, 30.0 mmol) and 3,3-dimethylglutaric anhydride (4.26 g, 30.0 mmol) was heated at 175 °C for 7 hours. After cooling down to room temperature the solid material was dissolved in a small amount of dichloromethane and purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane (40:60)) yielding the title compound (2.56 g, 34% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 1.20 (s, 6H), 2.69 (s, 4H), 3.95 (s, 3H), 3.81 (d, 1H), 7.28 (dd, 1H), 7.89 (d, 1H); HPLC-MS (Method A): *m/z* = 249 (M+H); *R<sub>t</sub>* = 2.43 min.

15 **N-(6-Methoxy-pyridin-3-yl)-2,2-dimethyl-propionamide hydrochloride**

5-Amino-2-methoxypyridine (3.72 g, 30.0 mmol), dissolved in a small amount of tetrahydrofuran, was added slowly to a solution of 2,2-dimethylpropionyl chloride (3.62 g, 30.0 mmol) in tetrahydrofuran (25 ml). After standing for 0.5 hours diethyl ether (250 ml) was added and a thick oil precipitated. The solvent was decanted and the residue was dried under reduced pressure yielding the title compound (5.50 g, 75% yield) as a purple foam.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 1.22 (s, 9H), 3.83 (s, 3H), 6.86 (d, 1H), 8.00 (dd, 1H), 8.42 (d, 1H), 9.41(s, 1H), 9.54 (br.s, 1H); HPLC-MS (Method A): *m/z* = 209 (M+H); *R<sub>t</sub>* = 2.28 min.

25 **2-Cyclohexyl-N-(6-methoxy-pyridin-3-yl)-acetamide hydrochloride**

5-Amino-2-methoxypyridine (3.72 g, 30.0 mmol), dissolved in a small amount of tetrahydrofuran, was added slowly to a solution of cyclohexylacetyl chloride (4.82 g, 30.0 mmol) in tetrahydrofuran (25 ml). After standing for 0.5 hours diethyl ether (250 ml) was added and the solids were collected by suction yielding the title compound (8.54 g, 100% yield) as a purple solid.

<sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>): δ 0.88-1.04 (m, H), 1.09-1.32 (m, 3H), 1.54-1.82 (m, 6H), 2.18 (d, 2H), 3.84 (s, 3H), 6.85 (d, 1H), 7.98 (dd, 1H), 8.41 (d, 1H), 9.81 (br.s, 1H), 10.10 (s, 1H); HPLC-MS (Method A): *m/z* = 249 (M+H); *R<sub>t</sub>* = 3.32 min.



***N*-(6-Hydroxy-pyridin-3-yl)-benzamide**

*N*-(6-Methoxy-pyridin-3-yl)-benzamide (2.38 g, 10.4 mmol) was dissolved in a mixture of tetrahydrofuran and diethyl ether. HCl-gas was bubbled into the solution for 5 minutes. More diethyl ether was added and the white precipitate was collected by suction, washed twice with diethyl ether and heated in a kugelrohr apparatus at 180 °C for 0.5 hours. The solid material was crystallised from methanol:water, washed twice with water and dried overnight in a vacuum oven, yielding the title compound (1.19 g, 53% yield) as a grey solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 6.39 (d, 1H), 7.47-7.61 (m, 3H), 7.18 (dd, 1H), 7.91 (d, 2H), 7.96 (d, 1H); HPLC-MS (Method A): *m/z* = 215 (M+H); R<sub>t</sub> = 1.52 min.

**Cyclohexanecarboxylic acid (6-hydroxy-pyridin-3-yl)-amide**

Cyclohexanecarboxylic acid (6-methoxy-pyridin-3-yl)-amide hydrochloride (8.12 g, 30.0 mmol) was heated in a kugelrohr apparatus at 190 °C for 25 minutes. After cooling to room temperature the solid material was crystallised from methanol:water, washed twice with water and dried overnight in a vacuum oven, yielding the title compound (3.09 g, 47% yield) as a purple solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 1.09-1.46 (m, 5H), 1.63 (m, 1H), 1.68-1.80 (m, 4H), 2.23 (m, 1H), 6.33 (d, 1H), 7.44 (dd, 1H), 7.87 (d, 1H), 9.54 (s, 1H), 11.29 (br.s, 1H); HPLC-MS (Method A): *m/z* = 221 (M+H); R<sub>t</sub> = 1.84 min.

**6'-Hydroxy-4,4-dimethyl-4,5-dihydro-3*H*-[1,3']bipyridinyl-2,6-dione**

6'-Methoxy-4,4-dimethyl-4,5-dihydro-3*H*-[1,3']bipyridinyl-2,6-dione (2.56 g, 10.3 mmol) was dissolved in a mixture of tetrahydrofuran and diethyl ether. HCl-gas was bubbled into the solution for 5 minutes. More diethyl ether was added and the white precipitate was collected by suction, washed twice with diethyl ether and heated in a kugelrohr apparatus at 190 °C for 15 minutes yielding the title compound (2.16 g, 89% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 1.08 (s, 6H), 2.52 (s, 4H), 6.34 (d, 1H), 7.19 (dd, 1H), 7.31 (d, 1H), 11.42 (br.s, 1H); HPLC-MS (Method A): *m/z* = 235 (M+H); R<sub>t</sub> = 1.32 min.

***N*-(6-Hydroxy-pyridin-3-yl)-2,2-dimethyl-propionamide**

Under a stream of nitrogen gas *N*-(6-methoxy-pyridin-3-yl)-2,2-dimethyl-propionamide hydrochloride (5.50 g, 22.5 mmol) was heated in a round bottom flask at 180 °C for 15 minutes. After cooling to room temperature the solid material was crystallised from a methanol-water mixture, yielding the title compound (1.13 g, 26% yield) as a dark grey solid.

- 5 <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 1.18 (s, 9H), 6.32 (d, 1H), 7.53 (dd, 1H), 7.76 (d, 1H), 8.97 (br.s, 1H), 11.30 (br.s, 1H); HPLC-MS (Method A): *m/z* = 195 (M+H); R<sub>t</sub> = 1.15 min.

### 2-Cyclohexyl-*N*-(6-hydroxy-pyridin-3-yl)-acetamide

- 10 2-Cyclohexyl-*N*-(6-methoxy-pyridin-3-yl)-acetamide hydrochloride (8.54 g, 30.0 mmol) was heated in a kugelrohr apparatus at 160 °C for 0.5 hours. After cooling to room temperature the solid material was crystallised from a methanol-water mixture, washed twice with water and dried overnight in a vacuum oven, yielding the title compound (4.53 g, 64% yield) as a grey solid.

- 15 <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 0.90-1.38 (m, 5H), 1.60-1.92 (m, 6H), 2.17 (d, 2H), 6.50 (d, 1H), 7.50 (dd, 1H), 7.97 (d, 1H), 8.80 (br.s, 1H), 11.81 (br.s, 1H); HPLC-MS (Method A): *m/z* = 235 (M+H); R<sub>t</sub> = 2.29 min.

### 3-Dimethylamino-2-(4-methoxy-phenoxy)-propenal

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Phosphorus oxychloride (18.4 g, 120 mmol) was added to dimethylformamide (8.8 g, 120 mmol), maintaining the temperature below 25 °C by an external ice-bath. Upon completion of the addition the reaction mixture was heated to 50 °C for 45 minutes and then cooled to room temperature. Chloroform (35 ml) was added and the resulting solution was brought to reflux.

- 25 4-Methoxyphenoxyacetaldehyde diethylacetal (9.61 g, 40.0 mmol) was added in portions. After heating for 3 hours at reflux the solution was cooled to room temperature and poured carefully onto a solution of potassium carbonate (115 g) in water (100 ml). The mixture was cooled in an ice-bath to around room temperature and extracted twice with dichloromethane. The combined organic layers were dried over sodium sulphate, filtered and evaporated *in vacuo* yielding a brown oil. The residue was heated with ethyl acetate:heptane and decanted, leaving a brown oil. The solvent was removed *in vacuo* to give a brown oil, which was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate) yielding the title compound (3.87 g, 44% yield) as a white solid.

- 30 <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 3.00 (s, 6H), 3.75 (s, 3H), 6.54 (s, 1H), 7.80 + 7.87 (AB-system, 4H), 8.80 (s, 1H); HPLC-MS (Method A): *m/z* = 222 (M+H); R<sub>t</sub> = 1.73 min.
- 35

**2-(3,4-Dichloro-phenoxy)-3-dimethylamino-propenal**

Phosphorus oxychloride (18.4 g, 120 mmol) was added to dimethylformamide (8.8 g, 120 mmol), maintaining the temperature below 25 °C by an external ice-bath. Upon completion of the addition the reaction mixture was heated to 50 °C for 45 minutes and then cooled to room temperature. Chloroform (35 ml) was added and the resulting solution was brought to reflux. 3,4-Dichlorophenoxyacetaldehyde diethylacetal (9.61 g, 40.0 mmol) was added in portions. After heating for 3 hours at reflux the solution was cooled to room temperature and poured carefully onto a solution of potassium carbonate (115 g) in water (100 ml). The mixture was cooled in an ice-bath to around room temperature and extracted twice with dichloromethane. The combined organic layers were dried over sodium sulphate, filtered and evaporated *in vacuo* yielding a brown oil, which was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate) yielding the title compound (5.38 g, 52% yield) as a brown solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 3.10 (s, 6H), 6.58 (s, 1H), 6.82 (dd, 1H), 7.03 (d, 1H), 7.30 (d, 1H), 8.80 (s, 1H); HPLC-MS (Method A): *m/z* = 260 (M+H); R<sub>t</sub> = 3.14 min.

**5-(4-Methoxy-phenoxy)-pyrimidin-2-ol**

A solution of sodium ethoxide, prepared from sodium (0.80 g, 35.0 mmol), 3-dimethylamino-2-(4-methoxy-phenoxy)-propenal (3.87 g, 17.5 mmol) and urea (2.10 g, 35.0 mmol) in ethanol (25 ml) was heated at reflux for 4 hours. Water (1 ml) was added and heating was continued for an additional 2 hours. The solution was cooled to room temperature and neutralised with glacial acetic acid. Most of the solvent was removed by evaporation *in vacuo*. Water was added and the precipitate was isolated by suction, followed by drying in a vacuum oven, yielding the title compound (0.80 g, 21% yield) as a yellow solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 3.80 (s, 3H), 6.85-7.95 (AB-system, 4H), 8.12 (s, 2H); HPLC-MS (Method A): *m/z* = 219 (M+H); R<sub>t</sub> = 1.77 min.

**5-(3,4-Dichloro-phenoxy)-pyrimidin-2-ol**

A solution of sodium ethoxide, prepared from sodium (0.95 g, 41.4 mmol), 2-(3,4-dichloro-phenoxy)-3-dimethylamino-propenal (5.38 g, 20.7 mmol) and urea (2.48 g, 41.4 mmol) in ethanol (25 ml) was heated at 60 °C for 4 hours. Water (1 ml) was added and heating was continued for an additional 2 hours. The solution was cooled to room temperature and neu-

tralised with glacial acetic acid. Most of the solvent was removed by evaporation *in vacuo*. Water was added and the precipitate was isolated by suction, followed by drying in a vacuum oven, yielding the title compound (0.92 g, 17% yield) as a brown solid.

<sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>): δ 7.08 (dd, 1H), 7.38 (d, 1H), 7.59 (d, 1H), 8.35 (s, 2H), 12.06 (br.s, 1H); HPLC-MS (Method A): *m/z* = 257 (M+H); *R*<sub>t</sub> = 2.75 min.

#### 5-(2-Nitro-phenyl)-pyrimidin-2-ol

10 A solution of 3-(dimethylamino)-2-(2-nitrophenyl)acrylaldehyde (2.00 g, 9.08 mmol), urea (0.60 g, 9.99 mmol) and concentrated hydrochloric acid (0.50 ml) in ethanol (25 ml) was heated at 60 °C for 18 hours under a nitrogen atmosphere. An additional aliquot of concentrated hydrochloric acid (0.50 ml) was added followed by heating at 70 °C for 24 hours. The solvent was removed by evaporation under reduced pressure. The residue was crystallised  
15 from methanol yielding the title compound (0.35 g, 18% yield) as a yellow solid.

<sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>): δ 7.54 (dd, 1H), 7.62 (dt, 1H), 7.76 (dt, 1H), 8.06 (dd, 1H), 8.29 (s, 2H); HPLC-MS (Method A): *m/z* = 218 (M+H); *R*<sub>t</sub> = 1.26 min.

#### 20 N-(6-Hydroxy-pyridin-3-yl)-3,3-dimethyl-butyramide

3,3-Dimethylbutyroyl chloride (4.04 g, 30.0 mmol) was added dropwise to a stirred solution of 5-amino-2-methoxypyridine (3.72 g, 30.0 mmol) in tetrahydrofuran (25 mL). After stirring for 1 hour at room temperature, diethyl ether was added and the solid material was isolated by  
25 suction. The *N*-(6-methoxy-pyridin-3-yl)-3,3-dimethyl-butyramide hydrochloride (4.13 g, 15.96 mmol) was heated at 180 °C for 15 minutes. After cooling to room temperature the product was dissolved in methanol. Partial evaporation of the solvent yielded the title compound (1.15 g, 35% yield) as a solid.

<sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>): δ = 1.00 (s, 9H), 2.12 (s, 2H), 6.38 (d, 1H), 7.44 (dd, 1H), 7.89 (d, 1H), 9.59 (s, 1H), 11.42 (br.s, 1H); HPLC-MS (Method A): *m/z* = 209 (M+H)<sup>+</sup>; *R*<sub>t</sub> = 1.71 min.

**Pyridine-2-carboxylic acid (6-methoxy-pyridin-3-yl)-amide dihydrochloride**

5-Amino-2-methoxypyridine (4.40 g, 35.4 mmol), dissolved in a small amount of tetrahydrofuran, was added slowly to a stirred solution of pyridine-2-carbonyl chloride hydrochloride (7.12 g, 40.0 mmol) in tetrahydrofuran (75 mL). After stirring overnight at room temperature diethyl ether was added. The solids were isolated by suction, washed with diethyl ether and dried in a vacuum oven at 45 °C, yielding the title compound (7.89 g, 75%).

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>):  $\delta$  = 3.87 (s, 3H), 6.90 (d, 1H), 7.03 (br.s, 2 HCl + H<sub>2</sub>O), 7.70 (m, 1H), 8.09 (dt, 1H), 8.17 (d, 1H), 8.22 (dd, 1H), 8.68 (d, 1H), 8.73 (m, 1H), 10.82 (s, 1H);

HPLC-MS (Method A):  $m/z$  = 230 (M+H)<sup>+</sup>; Rt = 2.45 min and 264 + 266; Rt = 3.15 min.

**Pyridine-2-carboxylic acid (6-hydroxy-pyridin-3-yl)-amide hydrochloride**

Pyridine-2-carboxylic acid (6-methoxy-pyridin-3-yl)-amide dihydrochloride (0.66 g, 1.99 mmol) was heated at 180 °C for 10 minutes. After cooling to room temperature, the title compound was obtained and used without further purification.

HPLC-MS (Method A):  $m/z$  = 216 (M+H)<sup>+</sup>; Rt = 2.14 min.

**5-Methoxy-pyrimidin-2-ylamine**

Under a nitrogen atmosphere phosphorus pentachloride (21 g, 0.10 mol) was added portionwise to 1,1,3-trimethoxyethane (12.0 g, 0.10 mol) with stirring and external cooling (ice-bath). After addition was completed, stirring was continued for an additional 30 minutes at room temperature. Dimethylformamide (22.5 mL) was added by means of a dropping funnel, while the reaction mixture was cooled externally with an ice-bath. After completion of the addition, the reaction mixture was heated at 60 °C for 70 minutes. The reaction mixture was then cooled in an ice-bath and methanol (50 mL) was added dropwise. The resulting solution was added dropwise to a stirred solution of sodium hydroxide (24 g) in methanol (80 mL) while cooling in an ice-bath. Guanidine nitrate (20.0 g, 0.16 mol) and sodium hydroxide (7.0 g, 0.175 mol) were added and the solution was stirred for 18 hours at room temperature. Water (150 mL) was added and the solution was extracted three times with dichloromethane.

The combined organic layers were evaporated *in vacuo* leaving a brown oil. According to <sup>1</sup>H NMR analysis a mixture of the desired product and the intermediate  $\beta$ -dimethylamine- $\alpha$ -methoxyacroleine was obtained. The mixture was dissolved in methanol (100 mL). Guanidine

nitrate (15.0 g, 0.12 mol) and sodium hydroxide (5.25 g, 0.13 mol) were added and the reaction mixture was heated at 60 °C for 3 hours, followed by stirring at room temperature for 3 days. Water was added and the solution was extracted three times with dichloromethane. The combined organic layers were dried over sodium sulphate, filtered and evaporated *in vacuo* yielding the title compound (5.43 g, 43% yield) as a yellow solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>):  $\delta$  = 3.80 (s, 3H), 5.08 (br.s, 2H), 8.04 (s, 2H); HPLC-MS (Method A):  $m/z$  = 126 (M+H)<sup>+</sup>; Rt = 0.39 min.

#### **1-(5-Methoxy-pyrimidin-2-yl)-4,4-dimethyl-piperidine-2,6-dione**

A mixture of 5-methoxy-pyrimidin-2-ylamine (1.00 g, 7.99 mmol) and 3,3-dimethylglutaric anhydride (1.14 g, 7.99 mmol) was heated at 180 °C for 9 hours. After cooling to room temperature the reaction mixture was dissolved in a small amount of dichloromethane and purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane 70:30), yielding the title compound (0.79 g, 40% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>):  $\delta$  = 1.23 (s, 6H), 2.67 (s, 4H), 3.97 (s, 3H), 8.48 (s, 2H); HPLC-MS (Method A):  $m/z$  = 250 (M+H)<sup>+</sup>; Rt = 1.86 min.

#### **1-(5-Hydroxy-pyrimidin-2-yl)-4,4-dimethyl-piperidine-2,6-dione**

A mixture of 1-(5-methoxy-pyrimidin-2-yl)-4,4-dimethyl-piperidine-2,6-dione (0.99 g, 3.97 mmol) and pyridine hydrochloride (1.50 g, 7.99 mmol) was heated at 190 °C for 2.5 hours. After cooling to room temperature the reaction mixture was dissolved in a small amount of dichloromethane and filtered over a short pad of silicagel and washed with ethyl acetate. Evaporation of the solvent *in vacuo* yielded the title compound (0.60 g, 64 % yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>):  $\delta$  = 1.23 (s, 6H), 2.65 (s, 4H), 8.42 (s, 2H), 9.94 (br.s, 1H); HPLC-MS (Method A):  $m/z$  = 236 (M+H)<sup>+</sup>; Rt = 1.53 min.

#### **6-Chloro-N-(6-hydroxy-pyridin-3-yl)-nicotinamide**

A solution of 6-chloro-nicotinoyl chloride (0.40 g, 2.27 mmol) and 5-amino-2-hydroxypyridine hydrochloride (0.33 g, 2.25 mmol) in dry tetrahydrofuran (15mL) was stirred at room tempera-

ture for 1 hour. Saturated sodium bicarbonate (aq) was added and the solution was extracted three times with dichloromethane. The combined organic layers were dried over sodium sulphate, filtered and evaporated *in vacuo*. The residue was dissolved in a mixture of methanol (10 mL) and aqueous sodium hydroxide (1N, 2 mL). After stirring for 2 hours at room temperature water was added and the solution was extracted with dichloromethane. The organic layer was dried over sodium sulphate, filtered and evaporated *in vacuo*, yielding the title compound which was used without further purification.

5 HPLC-MS (Method A):  $m/z = 250$  (M+H)<sup>+</sup>; Rt = 1.52 min.

### **N-(2,2-Dimethyl-propyl)-6-hydroxy-nicotinamide**

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A solution of 6-hydroxynicotinic acid (1.39 g, 10.0 mmol), 1-hydroxy-7-azabenzotriazole (1.50 g, 11.0 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.11 g, 11.0 mmol) in dimethylformamide (25 mL) was stirred at room temperature for 20 minutes. A solution of 2,2-dimethylpropylamine (0.96 g, 11.0 mmol) and *N,N*-diisopropylethylamine (1.42 g, 11.0 mmol) in a small amount of dimethylformamide was added. Stirring was continued for 15 0.5 hour at room temperature. Ethyl acetate was added and the reaction mixture was extracted twice with water. The solvent was evaporated *in vacuo* yielding the title compound, which was used without further purification.

HPLC-MS (Method A):  $m/z = 209$  (M+H)<sup>+</sup>; Rt = 1.86 min.

### **3-Chloro-6-(3,4-dichloro-phenoxy)-pyridazine**

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A solution of 3,6-dichloropyridazine (4.47 g, 30.0 mmol), 3,4-dichlorophenol (4.89 g, 30.0 mmol) and potassium hydroxide (1.68 g, 30.0 mmol) in dimethyl sulfoxide (20 mL) was heated at 60 °C overnight. The solvent was removed by evaporation *in vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane 50:50). Small amounts of starting material were removed by kugelrohr distillation. Crystallisation from ethyl acetate:heptane yielded the title compound (1.74 g, 21% yield) as a white solid.

25 <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>):  $\delta = 7.10$  (dd, 1H), 7.20 (d, 1H), 7.37 (d, 1H), 7.49 (d, 1H), 7.54 (d, 1H); HPLC-MS (Method A):  $m/z = 275$  and 277 (M+H)<sup>+</sup>; Rt = 4.00 min.

**6-(3,4-dichloro-phenoxy)-pyridazin-3-ol**

A solution of 3-chloro-6-(3,4-dichloro-phenoxy)-pyridazine (1.74 g, 6.32 mmol) in formic acid (25 mL) was heated at 100 °C for 3 hours. The solvent was removed by evaporation *in vacuo* yielding the title compound, which was used without further purification.

HPLC-MS (Method A):  $m/z$  = 257 (M+H)<sup>+</sup>; Rt = 3.13 min.

**(4-Hydroxy-piperidin-1-yl)-imidazol-1-yl-methanone**

A solution of 4-hydroxypiperidine (20.0 g, 198 mmol) and *N,N*-carbonyldiimidazole (32.06 g, 198 mmol) in tetrahydrofuran (250 mL) was heated overnight at reflux, followed by stirring at room temperature for two days. The solvent was evaporated yielding the title compound, which was used without further purification.

HPLC-MS (Method A):  $m/z$  = 196 (M+H)<sup>+</sup>; Rt = 0.39 min.

**[4-(tert-Butyl-dimethyl-silanyloxy)-piperidin-1-yl]-imidazol-1-yl-methanone**

tert-Butyldimethylsilyl chloride (30.14 g, 0.20 mol) was added to a stirred solution of (4-hydroxy-piperidin-1-yl)-imidazol-1-yl-methanone (39.05 g, 0.20 mol) in dimethylformamide (200 mL). After stirring for 3 days at room temperature, the solvent was removed by evaporation *in vacuo*. The residue was redissolved in dichloromethane, extracted twice with water, dried over sodium sulphate, filtered and evaporated *in vacuo*, yielding the title compound, which was used without further purification.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>):  $\delta$  = 0.07 (s, 6H), 0.90 (s, 9H), 1.64 (m, 2H), 1.81 (m, 2H), 3.53-3.74 (m, 4H), 4.06 (m, 1H), 7.07 (m, 1H), 7.18 (m, 1H), 7.86 (m, 1H); HPLC-MS (Method A):  $m/z$  = 310 (M+H)<sup>+</sup>; Rt = 3.40 min.

**3-[4-(tert-Butyl-dimethyl-silanyloxy)-piperidine-1-carbonyl]-1-methyl-3H-imidazol-1-ium iodide**

Methyl iodide (113.5 g, 0.80 mol) was added to a stirred solution of [4-(tert-butyl-dimethyl-silanyloxy)-piperidin-1-yl]-imidazol-1-yl-methanone (61.9 g, 0.20 mol) in acetonitrile (400 mL). After stirring overnight at room temperature the solvent was evaporated *in vacuo*. The resi-



due was washed with ethyl acetate:heptane and dried in a vacuum oven at 45 °C, yielding the title compound (60.92 g, 68% yield over three steps) as a white solid

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 0.08 (s, 6H), 0.88 (s, 9H), 1.57 (m, 2H), 1.83 (m, 2H), 3.45 (m, 2H), 3.65 (m, 2H), 3.93 (s, 3H), 4.06 (m, 1H), 7.87 (m, 1H), 8.03 (m, 1H), 9.56 (s, 1H);

5 HPLC-MS (Method A): m/z = 324 (M-I<sup>+</sup>); Rt = 2.95 min.

#### 4-Chloro-N-(6-hydroxy-pyridin-3-yl)-benzamide

4-Chlorobenzoyl chloride (1.75 g, 10.0 mmol) was added carefully to a stirred solution of 5-amino-2-methoxypyridine (1.24 g, 10.0 mmol) in dichloromethane (10 mL). After stirring  
10 overnight at room temperature, the solvent is evaporated *in vacuo* and the residue is heated in a pre-heated kugelrohr oven at 200 °C for 5-10 minutes under house-vacuum (around 20 mbar) yielding the title compound, which was used without further purification.

HPLC-MS (Method A): m/z = 249 (M+H)<sup>+</sup>; Rt = 2.18 min.

#### 4-Fluoro-N-(6-hydroxy-pyridin-3-yl)-benzamide

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Starting from 4-fluorobenzoyl chloride (1.59 g, 10.0 mmol) and using the procedure as described for the preparation of 4-Chloro-N-(6-hydroxy-pyridin-3-yl)-benzamide yielded the title compound, which was used without further purification.

HPLC-MS (Method A): m/z = 233 (M+H)<sup>+</sup>; Rt = 1.76 min.

#### 20 N-(6-Hydroxy-pyridin-3-yl)-3-methoxy-benzamide

Starting from 3-methoxybenzoyl chloride (1.71 g, 10.0 mmol) and using the procedure as described for the preparation of 4-Chloro-N-(6-hydroxy-pyridin-3-yl)-benzamide yielded the title compound, which was used without further purification.

25 HPLC-MS (Method A): m/z = 245 (M+H)<sup>+</sup>; Rt = 1.81 min.

**N-(6-Hydroxy-pyridin-3-yl)-4-methoxy-benzamide**

Starting from 4-methoxybenzoyl chloride (1.71 g, 10.0 mmol) and using the procedure as described for the preparation of 4-Chloro-N-(6-hydroxy-pyridin-3-yl)-benzamide yielded the title compound, which was used without further purification.

HPLC-MS (Method A):  $m/z$  = 245 (M+H)<sup>+</sup>; Rt = 1.72 min.

**N-(6-Hydroxy-pyridin-3-yl)-4-methoxy-benzamide**

Starting from 2,4-dichlorobenzoyl chloride (2.10 g, 10.0 mmol) and using the procedure as described for the preparation of 4-Chloro-N-(6-hydroxy-pyridin-3-yl)-benzamide yielded the title compound, which was used without further purification.

HPLC-MS (Method A):  $m/z$  = 283 (M+H)<sup>+</sup>; Rt = 2.28 min.

**N-(6-Hydroxy-pyridin-3-yl)-4-trifluoromethyl-benzamide**

Starting from 4-trifluoromethylbenzoyl chloride (2.09 g, 10.0 mmol) and using the procedure as described for the preparation of 4-Chloro-N-(6-hydroxy-pyridin-3-yl)-benzamide yielded the title compound, which was used without further purification.

HPLC-MS (Method A):  $m/z$  = 283 (M+H)<sup>+</sup>; Rt = 2.28 min.

**6'-Hydroxy-4,5-dihydro-3H-[1,3']bipyridinyl-2,6-dione**

Glutaric anhydride (1.14 g, 10.0 mmol) was added to a solution of 5-amino-2-methoxypyridine (1.24 g, 10.0 mmol) in dichloromethane (25 mL). After standing for 1 hour at room temperature, thionyl chloride (5.95 g, 50.0 mmol) was added, followed by heating to reflux for 0.5 hour. The solvent and excess thionyl chloride were evaporated *in vacuo*, yielding 4-(6-methoxy-pyridin-3-ylcarbonyl)-butyryl chloride, which was used without further purification.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>):  $\delta$  = 1.81 (quintet, 2H), 2.28 (t, 2H), 2.38 (t, 2H), 3.87 (s, 3H), 6.91 (d, 1H), 8.00 (dd, 1H), 8.43 (d, 1H), 10.24 (s, 1H, NH).; HPLC-MS (Method A):  $m/z$  = 253 (M+H)<sup>+</sup>; Rt = 1.94 min. (analysed as methyl ester).

The crude 4-(6-methoxy-pyridin-3-ylcarbamoyl)-butyryl chloride was redissolved in dichloromethane (25 mL). Thionyl chloride (5.95 g, 50 mmol) was added and the solution was heated to reflux overnight. The solvent and excess thionyl chloride were evaporated *in vacuo*, yielding 6'-methoxy-4,5-dihydro-3*H*-[1,3]bipyridinyl-2,6-dione hydrochloride, which was used

5 without further purification.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 2.00 (quintet, 2H), 2.72 (t, 4H), 3.88 (s, 3H), 6.90 (d, 1H), 7.51 (dd, 1H), 6.92 (d, 1H), 9.71 (br.s, HCl + H<sub>2</sub>O); HPLC-MS (Method A): *m/z* = 221 (M+H)<sup>+</sup>; Rt = 1.38 min.

The crude 6'-methoxy-4,5-dihydro-3*H*-[1,3]bipyridinyl-2,6-dione hydrochloride (2.57 g, 10.0 mmol) was heated in a pre-heated kugerohr oven at 180 °C for 5 minutes. After cooling to room temperature the product was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:acetone 25:75), yielding the title compound (0.48 g, 23% yield) as a white solid.

10 <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 2.10 (quintet, 2H), 2.81 (t, 4H), 3.53 (br.s, 3H), 7.12 (br.s, 1H), 7.27 (m, 1H), 7.38 (m, 4H), 7.50 (d, 1H), 8.09 (s, 1H); HPLC-MS (Method A): *m/z* = 340 (M+H)<sup>+</sup>; Rt = 2.89 min.

#### 1-(6-Methoxy-pyridin-3-yl)-pyrrolidine-2,5-dione

A mixture of 5-amino-2-methoxypyridine (1.24 g, 10.0 mmol) and succinic anhydride (1.00 g, 10.0 mmol) was heated with a heat gun for 10 minutes. After cooling to room temperature the product was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:acetone 25:75).

20 Evaporation of the solvent yielded the title compound as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 2.92 (s, 4H), 3.96 (s, 3H), 6.82 (d, 1H), 7.50 (dd, 1H), 8.11 (d, 1H); HPLC-MS (Method A): *m/z* = 207 (M+H)<sup>+</sup>; Rt = 1.26 min.

#### 1-(6-Hydroxy-pyridin-3-yl)-pyrrolidine-2,5-dione

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1-(6-Methoxy-pyridin-3-yl)-pyrrolidine-2,5-dione was dissolved in tetrahydrofuran and HCl-gas was bubbled into the solution for 5 minutes. The solvent was evaporated *in vacuo* and the residue was heated for 10 minutes at 180 °C in a pre-heated kugelrohr oven. After cooling to room temperature the residue was purified by flash column chromatography (SiO<sub>2</sub>), yielding the title compound (285 mg, 15% yield over two steps).

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<sup>1</sup>H NMR (400MHz, DMSO-*d*<sub>6</sub>): δ = 2.72 (s, 4H), 6.40 (d, 1H), 7.31 (dd, 1H), 7.39 (d, 1H), 11.76 (br.s, 1H, OH); HPLC-MS (Method A): *m/z* = 193 (M+H)<sup>+</sup>; Rt = 0.37 min.

**2-Methoxy-5-(5-trifluoromethyl-pyridin-2-yloxy)-pyridine**

A solution of 5-hydroxy-2-methoxypyridine (1.25 g, 10.0 mmol), 2-chloro-5-trifluoromethylpyridine (1.82 g, 10.0 mmol) and potassium hydroxide (85% pure, 1.08 g, 10.0 mmol) in dimethyl sulfoxide (25 mL) was heated at 90 °C for 2.5 hours. The solution was cooled to room temperature and poured slowly into water (200 mL). After cooling with an external ice-bath, the precipitate was collected by suction, washed thoroughly with water and dried in a vacuum oven at 45 °C, yielding the title compound (2.56 g, 95% yield).

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 3.95 (s, 3H), 6.80 (d, 1H), 7.04 (d, 1H), 7.41 (dd, 1H), 7.91 (dd, 1H), 8.03 (d, 1H), 8.40 (d, 1H); HPLC-MS (Method A): *m/z* = 271 (M+H)<sup>+</sup>; Rt = 3.88 min.

**5-(5-Trifluoromethyl-pyridin-2-yloxy)-pyridin-2-ol**

A mixture of 2-methoxy-5-(5-trifluoromethyl-pyridin-2-yloxy)-pyridine (0.28 g, 1.04 mmol) and pyridine hydrochloride (1.00 g, 8.65 mmol) was heated in a kugelrohr oven at 200 °C for 10 minutes. After cooling to room temperature, the reaction mixture is dissolved in dichloromethane and extracted with water, dried over sodium sulphate, filtered and evaporated *in vacuo*, yielding the title compound (180 mg, 68% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 6.63 (m, 1H), 7.06 (d, 1H), 7.42 (m, 2H), 7.92 (dd, 1H), 8.42 (d, 1H); HPLC-MS (Method A): *m/z* = 257 (M+H)<sup>+</sup>; Rt = 2.32 min.

**5-(3,5-Dichloro-pyridin-2-yloxy)-2-methoxy-pyridine**

A solution of 5-hydroxy-2-methoxypyridine (1.25 g, 10.0 mmol), 2,3,5-trichloropyridine (1.82 g, 10.0 mmol) and potassium hydroxide (85% pure, 1.08 g, 10.0 mmol) in dimethyl sulfoxide (25 mL) was heated at 90 °C for 1.5 hours. The solution was poured slowly into water (200 mL). The precipitate was collected by suction, washed thoroughly with water and dried in a vacuum oven at 45 °C, yielding the title compound (2.39 g, 88% yield).

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 3.95 (s, 3H), 6.80 (d, 1H), 7.41 (dd, 1H), 7.77 (d, 1H), 7.93 (d, 1H), 8.03 (d, 1H); HPLC-MS (Method A): *m/z* = 271 (M+H)<sup>+</sup>; Rt = 4.18 min.

**5-(3,5-Dichloro-pyridin-2-yloxy)-pyridin-2-ol**

A mixture of 5-(3,5-dichloro-pyridin-2-yloxy)-2-methoxy-pyridine (2.39 g, 8.82 mmol) and pyridine hydrochloride (7.00 g, 60.6 mmol) was heated in a kugelrohr apparatus at 200 °C for 25 minutes. After cooling to room temperature dichloromethane and water were added. The solid material, which was insoluble in dichloromethane and water, was isolated by suction and dried in a vacuum oven at 45 °C, yielding the title compound, which was used without further purification.

HPLC-MS (Method A):  $m/z$  = 257 (M+H)<sup>+</sup>; Rt = 2.53 min.

**4,4-Dimethyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-6'-ol**

Under a nitrogen atmosphere lithium aluminium hydride (1.90 g, 50.0 mmol) was added portionwise to a stirred suspension of 6'-methoxy-4,4-dimethyl-4,5-dihydro-3H-[1,3']bipyridinyl-2,6-dione (2.85 g, 10.0 mmol) in dry diethyl ether (100 mL). After stirring for 3 hours at room temperature, water (1.90 mL), 15% aqueous sodium hydroxide (1.90 mL) and water (5.70 mL) were added respectively. After stirring for 1 hour at room temperature the salts were removed by filtration and washed three times with diethyl ether. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (SiO<sub>2</sub>, dichloromethane followed by ethyl acetate/heptane 25/75) yielding the title compound (1.28 g, 58% yield) as a yellow oil.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>):  $\delta$  = 0.98 (s, 6H), 1.53 (m, 4H), 3.03 (m, 4H), 3.89 (s, 3H), 6.67 (d, 1H), 7.30 (dd, 1H), 7.80 (d, 1H); HPLC-MS (Method A):  $m/z$  = 221 (M+H)<sup>+</sup>; Rt = 2.14 min.

**4,4-Dimethyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-6'-ol**

A mixture of 6'-methoxy-4,4-dimethyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl (1.28 g, 5.81 mmol) and pyridine hydrochloride (5.00 g, 43.3 mmol) was heated in a kugelrohr oven at 200 °C for 15 minutes. After cooling to room temperature water was added and the solution was made slightly basic with aqueous 1N sodium hydroxide. The solution was extracted three times with dichloromethane and the combined organic layers were dried over sodium sulphate, filtered and evaporated *in vacuo*, yielding the title compound (0.86 g, 72% yield).

HPLC-MS (Method A):  $m/z$  = 207 (M+H)<sup>+</sup>; Rt = 1.31 min.

**Methyl-phenyl-carbamic acid 4-amino-phenyl ester**

To a solution of N-Boc protected 4-aminophenol (10 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added N-methyl-N-phenylcarbonyl chloride (15 mmol) and DABCO (15 mmol) at room temperature. The reaction mixture was stirred for 16 hours at rt, added CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and washed with  
5 aqueous citric acid (5%) and brine. The organic phase was separated, dried (MgSO<sub>4</sub>) and evaporated to give the crude product which was purified by FC (Quad flash 40 MeOH-CH<sub>2</sub>Cl<sub>2</sub> 5:95). The purified intermediate was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (90 mL). Addition of TFA (6 mL) and stirring for 4 h. The reaction mixture was evaporated to dryness and dried in vacuo at 50 °C overnight producing the title compound in 72% yield as colorless crystals.

10 HPLC-MS : *m/z* = 243.1 (M+1); *R<sub>t</sub>* = 2.02 min.

**Example 1 (General procedure 9)**

15 4-[(1,3-Benzodioxol-5-yl)methyl]-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-piperonylpiperazine, yield 67 %. Recrystallisation from 96 % ethanol gave white crystals, m.p. 239 - 240 °C; HPLC-MS *m/z* = 502 (M+H), 524 (M+Na),

20 *R<sub>t</sub>* = 3.3 min.; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 11.64 (br, 1H, NH), 8.62 - 8.52 (br, 1H, py-H6), 8.31 - 8.19 (m, 1H, py-H4), 7.40 - 7.15 (m, 6H, py-H3 + C<sub>6</sub>H<sub>4</sub> + 1 arom.), 7.15 - 6.93 (m, 2H, arom), 4.53 - 3.96 (br, 4H, CH<sub>2</sub> at 4.26 + 2 CH), 3.80 - 2.89 (br, 6H, water at 3.38 + 4C-H); IR (KBr): ν 1724 (C=O).

**Example 2 (General procedure 1)**

Methyl-phenyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and N-methyl-N-phenylcarbonyl chloride. The crude product was purified by preparative HPLC  
30 (36%, white crystals). HPLC-MS *m/z* = 389.1 (M+1), *R<sub>t</sub>*: 5.13 min.

δ<sub>H</sub>(300MHz; CDCl<sub>3</sub>): 3.43 (s, 3H), 6.98 (d, 1H, J 8.7), 7.09-7.22 (m, 4H), 7.30-7.34 (m, 1H), 7.35 (d, 2H, J 7.1), 7.40 (t, 2H, J 6.8), 7.88 (dd, 1H, J 8.7 and 2.3), 8.42 (s, 1H).

**Example 3 (General procedure 1)**

35 Methyl-phenyl-carbamic acid 3-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 3-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and N-methyl-N-phenylcarbonyl chloride. The crude product was subjected to flash chromatography (Quad flash 25, dichloromethane) (89%, oil). HPLC-MS  $m/z$  = 389.1 (M+1), Rt: 5.08 min.  $\delta_H$ (300MHz; DMSO- $d_6$ ): 3.34 (s, 3H), 7.00-7.15 (m, 3H), 7.27 (t, 2H), 7.35-7.55 (m, 5H), 8.24 (dd, 1H), 8.58 (s, 1H).

**Example 4** (General procedure 1)

Methyl-phenyl-carbamic acid 4-(3,5-dichloro-pyridin-2-yloxy)-phenyl ester

- 10 The title compound was prepared from 4-(3,5-dichloro-pyridin-2-yloxy)-phenol and N-methyl-N-phenylcarbonyl chloride. The crude product was purified by preparative HPLC (53%, crystals). HPLC-MS  $m/z$  = 389.1 (M+1), Rt: 5.1 min.  $\delta_H$ (300MHz;  $CDCl_3$ ): 3.43 (s, 3H), 7.07-7.20 (m, 4H), 7.27-7.48 (m, 5H), 7.75 (d, 1H, J 2.2), 7.93 (d, 1H, J 2.2).

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**Example 5** (General procedure 1)

Methyl-phenyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-ylamino)-phenyl ester

- 20 The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-ylamino)-phenol and N-methyl-N-phenylcarbonyl chloride. The crude product was purified by preparative HPLC to give the title product (32%, white crystals). HPLC-MS  $m/z$  = 388.2 (M+1), Rt: 4.72 min.  $\delta_H$ (300MHz;  $CDCl_3$ ): 3.44 (s, 3H), 6.76 (d, 1H), 6.81 (bs, 1H), 7.12 (d, 2H), 7.27-7.45 (m, 6H), 7.63 (dd, 1H), 8.42 (bs, 1H).

- 25 **Example 6** (General procedure 1)

Methyl-phenyl-carbamic acid 4-(3,5-dichloro-pyridin-4-yloxy)-phenyl ester

- 30 The title compound was prepared from 4-(3,5-dichloro-pyridine-4-yloxy)-phenol and N-methyl-N-phenylcarbonyl chloride. The crude product was purified by preparative HPLC (41%, white crystals). HPLC-MS  $m/z$  = 389.1 (M+1), Rt: 4.97 min.  $\delta_H$ (300MHz;  $CDCl_3$ ): 3.42 (s, 3H), 6.81 (d, 2H, J 9.0), 7.07 (d, 2H, J 7.9), 7.25-7.43 (M, 5H), 8.55 (s, 2H).

**Example 7** (General procedure 1)

**Methyl-phenyl-carbamic acid 4-(4-trifluoromethyl-phenoxy)-phenyl ester**

The title compound was prepared from 4-(4-trifluoromethyl-phenoxy)-phenol and N-methyl-N-phenylcarbamoil chloride. The crude product was purified by preparative HPLC (78%, white crystals). HPLC-MS  $m/z$  = 388.0 (M+1), Rt: 5.59 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 3.43 (s, 3H), 7.02 (d, 4H, J 8.7), 7.14 (d, 2H, J 8.7), 7.31 (1H, d, J 6.8), 7.35 (d, 2H, J 7.2), 7.41 (t, 2H, J 7.1), 7.55 (d, 2H, J 8.6).

**Example 8 (General procedure 1)****Methyl-phenyl-carbamic acid 4-(3-trifluoromethyl-phenoxy)-phenyl ester**

The title compound was prepared from 4-(3-trifluoromethyl-phenoxy)-phenol and N-methyl-N-phenylcarbamoil chloride. The crude product was purified by preparative HPLC (73%, white crystals). HPLC-MS  $m/z$  = 388.2 (M+1), Rt: 5.37 min.

**Example 9 (General procedure 1)****Methyl-phenyl-carbamic acid 4-(2-cyano-5-trifluoromethyl-pyridine-3-yloxy)-phenyl ester**

The title compound was prepared from 4-(2-cyano-5-trifluoromethyl-pyridin-3-yloxy)-phenol and N-methyl-N-phenylcarbamoil chloride. The crude product was purified by preparative HPLC (74%, colourless oil). HPLC-MS  $m/z$  = 414.1 (M+1), Rt: 4.8 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 3.44 (s, 3H), 7.11 (d, 2H, J 9), 7.32-7.1 (m, 3H), 7.32-7.50 (m, 5H), 8.63 (s, 1H).

**Example 10 (General procedure 1)****Methyl-phenyl-carbamic acid 2-benzenesulfonyl-4-(3-chloro-5-trifluoromethyl-pyridine-2-yloxy)-phenyl ester**

The title compound was prepared from 2-benzenesulfonyl-4-(3-chloro-5-trifluoromethyl-pyridine-2-yloxy)-phenol and N-methyl-N-phenylcarbamoil chloride. The crude product was purified by preparative HPLC (68%, white crystals). HPLC-MS  $m/z$  = 563.1 (M+1), Rt: 5.3 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 3.44 (s, 3H), 7.20-7.50 (m, 12H), 7.91 (bs, 1H), 8.00 (d, 1H, J 2.3), 8.23 (s, 1H).



**Example 11** (General procedure 1)**Methyl-phenyl-carbamic acid 4-tert-butoxy-phenyl ester**

The title compound was prepared from 4-tert-butoxy-phenol and N-methyl-N-phenylcarbonyl chloride. The crude product was subjected to flash chromatography (Quad12/25, flash 12, dichloromethane) followed by a recrystallization from ethanol (41%, crystals). HPLC-MS  $m/z$  = 300.3 (M+1), Rt: 4.7 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 1.31 (s, 9H), 3.41 (s, 3H), 6.90-7.07 (m, 4H), 7.20-7.28 (m, 1H), 7.32-7.43 (m, 4H).

**Example 12** (General procedure 1)**Methyl-phenyl-carbamic acid 3-(4-fluorobenzyl)-4-methyl-2-oxo-2H-chromen-7-yl ester**

The title compound was prepared from 3-(4-fluorobenzyl)-7-hydroxy-4-methyl-2H-chromen-2-one and N-methyl-N-phenylcarbonyl chloride.

The crude product was of high purity and tested without purification ( $\approx$  100%, crystals); mp: 185-186°C. HPLC-MS  $m/z$  = 418.2 (M+1), Rt: 5.2 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 2.43 (s, 3H), 3.43 (s, 3H), 6.95 (dt, 2H, J 8.7 and 2.3), 7.10 (m, 2H), 7.21 (dt, 2H, J 7.2 and 2.3), 7.27-7.45 (m, 5H), 7.58 (d, 1H, J 8.3).

**Example 13** (General procedure 1)**Methyl-phenyl-carbamic acid 4-phenoxy-phenyl ester**

The title compound was prepared from 4-phenoxy-phenol and N-methyl-N-phenylcarbonyl chloride. The crude product was recrystallized (ethanol/water) (86%, white crystals). HPLC-MS  $m/z$  = 320.1 (M+1), Rt: 5.13 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 3.43 (s, 3H), 6.94-7.02 (m, 4H), 7.08 (t, 2H, J 6.8), 7.04-7.12 (m, 1H), 7.32 (t, 2H, J 7.5), 7.28-7.35 (m, 1H), 7.35-7.45 (m, 4H).

**Example 14** (General procedure 1)**Methyl-phenyl-carbamic acid 4-(4-chlorobenzoyl)-phenyl ester**

The title compound was prepared from 4-(4-chlorobenzoyl)-phenol and N-methyl-N-phenylcarbonyl chloride. The crude product was recrystallized (ethanol/water) (90%, white crystals). HPLC-MS  $m/z$  = 366.1 (M+1), Rt: 5.19 min.

$\delta_{\text{H}}$ (300MHz;  $\text{CDCl}_3$ ): 3.45 (s, 3H), 7.19-7.37 (m, 4H), 7.40 (t, 2H, J 7.2), 7.37-7.40 (m, 1H), 7.46 (dt, 2H, J 8.7 and 2.3), 7.73 (dt, 2H, J 8.7 and 2.2), 7.79 (d, 2H, J 8.7).

**Example 15** (General procedure 1)

5 Methyl-phenyl-carbamic acid 4-(3-chloro-5-trifluoromethyl)-pyridine-2-yloxy)-phenyl ester

The title compound was prepared from 4-(3-chloro-5-trifluoromethyl)-pyridine-2-yloxy)-phenol and N-methyl-N-phenylcarbonyl chloride. Prepared as described in general procedure 1.

The crude product was recrystallized (ethanol/water (78%, white crystals). HPLC-MS  $m/z$  =  
10 423.1 (M+1), Rt: 5.31 min.

$\delta_{\text{H}}$ (300MHz;  $\text{CDCl}_3$ ): 3.43 (s, 3H), 7.10-7.23 (m, 4H), 7.27 (t, 1H, J 6.8), 7.35 (d, 2H, J 7.5), 7.41 (t, 2H, J 7.4), 7.96 (d, 1H, J 1.9), 8.23 (bs, 1H).

**Example 16** (General procedure 1)

15 Methyl-phenyl-carbamic acid 4-[4-(4-chloro-phenyl)-thiazol-2-yl]-phenyl ester

The title compound was prepared from 4-[4-(4-chloro-phenyl)-thiazol-2-yl]-phenol and N-methyl-N-phenylcarbonyl chloride. The crude product was recrystallized (ethanol/water) (59%, white crystals). HPLC-MS  $m/z$  = 421.1 (M+1), Rt: 5.85 min

20  $\delta_{\text{H}}$ (300MHz;  $\text{CDCl}_3$ ): 3.45 (s, 3H), 7.18-7.25 (m, 2H), 7.27-7.33 (m, 1H), 7.34-7.41 (m, 4H), 7.43 (d, 2H, J 6.8), 7.41-7.46 (m, 1H), 7.92 (dt, 2H, J 8.6 and 2.2), 8.00 (d, 2H, J 8.7).

**Example 17** (General procedure 1)

Methyl-phenyl-carbamic acid 4-pyrrol-1-yl-phenyl ester

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The title compound was prepared from 4-pyrrol-1-yl-phenol and N-methyl-N-phenylcarbonyl chloride. The crude product was recrystallized (ethanol/water) (27%, off-white crystals). HPLC-MS  $m/z$  = 293.2 (M+1), Rt: 4.51 min.

$\delta_{\text{H}}$ (300MHz;  $\text{CDCl}_3$ ): 3.44 (s, 3H), 6.33 (t, 2H, J 2.2), 7.03 (t, 2H, J 2.2), 7.17 (bd, 2H, J 8.3),  
30 7.29 (d, 1H, J 6.8), 7.31-7.38 (m, 4H), 7.41 (t, 2H, J 6.8).

**Example 17a** (General procedure 1)

Methyl-phenyl-carbamic acid 4-imidazol-1-yl-phenyl ester

35 The title compound was prepared from 4-imidazol-1-yl-phenol and N-methyl-N-

phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (4%, clear oil). HPLC-MS  $m/z$  = 294.1 ( $M+1$ ), Rt: 2.25 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 3.44 (s, 3H), 7.27-7.39 (m, 4H), 7.39-7.50 (m, 5H), 7.53 (bs, 1H), 8.83 (bs, 1H).

5

**Example 18** (General procedure 1)

Methyl-phenyl-carbamic acid 4-(3-chloro-5-trifluoromethyl)-pyridine-2-ylmethyl)-phenyl ester

The title compound was prepared from 4-(3-chloro-5-trifluoromethyl)-pyridine-2-ylmethyl)-phenol and N-methyl-N-phenylcarbamoyl chloride.

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The crude product was recrystallized (ethanol/water) (74%, white crystals). HPLC-MS  $m/z$  = 421.1 ( $M+1$ ), Rt: 5.23 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 3.40 (s, 3H), 4.33 (s, 2H), 7.03 (d, 2H, J 8.3), 7.20-7.30 (m, 3H), 7.3 (d, 2H, J 7.2), 7.38 (t, 2H, J 7.2), 7.87 (d, 1H, J 1.5), 8.69 (bs, 1H).

15

**Example 19** (General procedure 1)

Methyl-phenyl-carbamic acid 4-trifluoromethylsulfanyl-phenyl ester

The title compound was prepared from 4-trifluoromethylsulfanyl-phenol and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (70%, clear oil). HPLC-MS  $m/z$  = 328.0 ( $M+1$ ), Rt: 5.16 min.

20

$\delta_H$ (300MHz;  $CDCl_3$ ): 3.42 (s, 3H), 7.19 (d, 2H, J 6.4), 7.26-7.7.37 (m, 3H), 7.41 (t, 2H, J 7.9), 7.63 (d, 2H, J 8.3).

25

**Example 20** (General procedure 1)

Methyl-phenyl-carbamic acid 4-pentafluoromethyloxy-phenyl ester

The title compound was prepared from 4-pentafluoromethyloxy-phenol and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (66%, clear oil). HPLC-MS  $m/z$  = 362.0 ( $M+1$ ), Rt: 5.31 min.

30

$\delta_H$ (300MHz;  $CDCl_3$ ): 3.42 (s, 3H), 7.10-7.22 (m, 4H), 7.29 (d, 1H, J 7.2), 7.34 (d, 2H, J 7.1), 7.41 (t, 2H, J 7.1).

**Example 21** (General procedure 1)

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Methyl-phenyl-carbamic acid 4-benzyloxy-phenyl ester

The title compound was prepared from 4-benzyloxy-phenol and N-methyl-N-phenylcarbamoyl chloride. The crude product was recrystallized (ethanol/water) (83%, white crystals). HPLC-MS  $m/z$  = 334.2 (M+1), Rt: 4.88 min.

5  $\delta_H$ (300MHz;  $CDCl_3$ ): 3.41 (s, 3H), 5.03 (s, 2H), 6.92 (dt, 2H, J 9.0 and 2.2), 7.02 (d, 2H, J 8.7), 7.26-7.34 (m, 2H), 7.34-7.38 (m, 4H), 7.38-7.44, m, 4H).

**Example 22** (General procedure 1)

Methyl-phenyl-carbamic acid 4-benzyl-phenyl ester

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The title compound was prepared from 4-benzyl-phenol and N-methyl-N-phenylcarbamoyl chloride. The crude product was recrystallized (ethanol/water) (56%, white crystals). HPLC-MS  $m/z$  = 318.1 (M+1), Rt: 5.05 min.

15  $\delta_H$ (300MHz;  $CDCl_3$ ): 3.41 (s, 3H), 3.95 (s, 2H), 7.02 (d, 2H), 7.12-7.19 (m, 5H), 7.20-7.25 (m, 2H), 7.26-7.28 (m, 1H), 7.28-7.34 (m, 1H), 7.34-7.42 (m, 3H).

**Example 23** (General procedure 1)

Methyl-phenyl-carbamic acid 4'-cyano-biphenyl-4-yl-ester

20 The title compound was prepared from 4-hydroxy-4'-biphenylcarbonitrile and N-methyl-N-phenylcarbamoyl chloride applying procedure 1. The crude product was recrystallized (ethanol/water) (87%, white crystals). HPLC-MS  $m/z$  = 329.2 (M+1), Rt: 4.63 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 3.44 (s, 3H), 7.18-7.26 (m, 2H), 7.26-7.32 (m, 2H), 7.34-7.46 (m, 4H), 7.56 (d, 2H), 7.64 (d, 2H), 7.712 (d, 2H).

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**Example 24** (General procedure 1)

Methyl-phenyl-carbamic acid 4'-bromo-biphenyl-4-yl-ester

30 The title compound was prepared from 4-bromo-4'-hydroxybiphenyl and N-methyl-N-phenylcarbamoyl chloride. The crude product was recrystallized (ethanol) (72%, white crystals). HPLC-MS  $m/z$  = 382.0 (M+1), Rt: 5.41 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 3.44 (s, 3H), 7.15-7.23 (d, 2H), 7.26-7.31 (m, 1H), 7.34-7.45 (m, 6H), 7.47.7.57 (m, 4H).

35 **Example 25** (General procedure 1)

**Methyl-phenyl-carbamic acid biphenyl-4-yl-ester**

The title compound was prepared from 4-hydroxybiphenyl and N-methyl-N-phenylcarbamoyl chloride applying. The crude product was recrystallized (ethanol) (75%, white crystals).

5 HPLC-MS  $m/z$  = 304.2 ( $M+1$ ), Rt: 4.95 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 3.45 (s, 3H), 7.19 (d, 2H), 7.26-7.37 (m, 2H), 7.37-7.46 (m, 6H), 7.55 (d, 4H).

**Example 26 (General procedure 1)**

10 Methyl-phenyl-carbamic acid 4-[3-(4-chlorophenyl)-ureido]-phenyl ester

The title compound was prepared from 4-[3-(4-chlorophenyl)-ureido]-phenol and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (33%, off-white crystals). HPLC-MS  $m/z$  = 396.1 ( $M+1$ ), Rt: 4.40 min.

15  $\delta_H$ (300MHz;  $CDCl_3$ ): 3.52 (s, 3H), 6.85-7.03 (m, 7H), 7.09 (d, 2H), 7.30-7.50 (m, 6H).

**Example 27 (General procedure 1)**

Methyl-phenyl-carbamic acid 4-(4-nitro-phenoxy)-phenyl ester

20 The title compound was prepared from 4-(4-nitro-phenoxy)-phenol and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (71%, white crystals). HPLC-MS  $m/z$  = 365.0 ( $M+1$ ), Rt: 4.83 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 3.44 (s, 3H), 7.00 (d, 2H), 7.06 (d, 2H), 7.26-7.32 (m, 1H), 7.33-7.49 (m, 4H), 8.20 (dt, 2H).

25

**Example 28 (General procedure 1)**

Methyl-phenyl-carbamic acid 4-heptylsulfanyl-phenyl ester

30 The title compound was prepared from 4-heptylsulfanyl-phenol and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (74%, colourless oil, HPLC-MS  $m/z$  = 358.2 ( $M+1$ ), Rt: 6.21 min.

$\delta_H$ (200MHz;  $CDCl_3$ ): 0.87 (t, 3H), 1.15-1.50 (m, 8H), 1.50-1.75 (m, 2H), 2.86 (t, 2H), 3.41 (s, 3H), 7.04 (d, 2H), 7.15-7.50 (m, 7H).

35 **Example 29 (General procedure 1)**

**Methyl-phenyl-carbamic acid 4-butoxy-phenyl ester**

The title compound was prepared from 4-butoxy-phenol and N-methyl-N-phenylcarbamoil chloride. The crude product was recrystallized from ethanol (22%, white crystals). HPLC-MS

5  $m/z = 300.1$  (M+1), Rt: 5.20.

$\delta_H$ (300MHz;  $CDCl_3$ ): 0.96 (t, 3H), 1.45 (qi, 2H), 1.74 (qi, 2H), 3.41 (s, 3H), 3.92 (t, 2H), 6.84 (d, 2H), 6.99 (d, 2H), 7.25-7.27 (m, 1H), 7.30-7.45 (m, 4H).

**Example 30 (General procedure 1)**

10 **Methyl-phenyl-carbamic acid 4-(4-chloro-benzenesulfonyl)-phenyl ester**

The title compound was prepared from 4-(4-chloro-benzenesulfonyl)-phenol and N-methyl-N-phenylcarbamoil chloride. The crude product was subjected to preparative HPLC (46%, colourless oil). HPLC-MS  $m/z = 402.1$ (M+1), Rt: 4.65 min.

15  $\delta_H$ (200MHz;  $CDCl_3$ ): 3.41 (s, 3H), 7.21-7.35 (m, 5H), 7.39 (d, 2H), 7.46 (dt, 2H), 7.84 (dt, 2H), 7.90 (d, 2H).

**Example 31 (General procedure 1)**

20 **Methyl-phenyl-carbamic acid 4-(4-chloromethyl-thiazol-2-yl)-phenyl ester**

The title compound was prepared from 4-(4-chloromethyl-thiazol-2-yl)-phenol and N-methyl-N-phenylcarbamoil chloride. The aqueous phase was adjusted to PH 7.0 (phosphate buffer) before extraction with ethyl acetate. The crude product was subjected to preparative HPLC (21%, white crystals). HPLC-MS  $m/z = 359.0$  (M+1), Rt: 4.60.

25  $\delta_H$ (200MHz;  $CDCl_3$ ): 3.44 (s, 3H), 4.73 (s, 2H), 7.20 (bd, 2H), 7.26-7.48 (m, 6H), 7.92 (bd, 2H).

**Example 32 (General procedure 3)**

30 **Methyl-phenyl-carbamic acid 4-(4,4-dimethyl-2,6-dioxo-piperidin-1-yl)-phenyl ester**

The title product was prepared from 1-(4-hydroxyphenyl)-4,4-dimethylpiperidine-2,6-dione (233 mg, 1.00 mmol) ) and 1-methyl-3-(methyl-phenyl-carbamoyl)-3H-imidazol-1-ium iodide (343 mg, 1.00 mmol) by applying general procedure 3 (192 mg, 52%, white solid). HPLC-MS  $m/z = 367$  (M+1);  $R_t = 3.78$  min.

35  $^1H$  NMR (300MHz,  $CDCl_3$ ):  $\delta$  1.19 (s, 6H), 2.65 (s, 4H), 3.42 (s, 3H), 7.03 (d, 2H), 7.15-7.43

(m, 7H).

**Example 33** (General procedure 3)

*cis*-Methyl-phenyl-carbamic acid 4-(1,3-dioxo-octahydro-isoindol-2-yl)-phenyl ester

5

The title compound (293 mg, 77% yield, white crystals) was prepared from *cis*-2-(4-hydroxy-phenyl)hexahydroisoindole-1,3-dione (245 mg, 1.00 mmol) and 1-methyl-3-(methyl-phenyl--carbamoyl)-3*H*-imidazol-1-ium iodide (343 mg, 1.00 mmol). HPLC-MS *m/z* = 379 (M+1); *R*<sub>t</sub> = 4.08 min.

10 <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 1.50 (m, 4H), 1.90 (m, 4H), 3.00 (m, 1H), 3.42 (s, 3H), 7.13-7.44 (m, 9H).

**Example 34** (General procedure 3)

Methyl-phenyl-carbamic acid 4-(cyclohexanecarbonyl-amino)-phenyl ester

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The title compound (283 mg, 80% yield, white crystals) was prepared from cyclohexanecarboxylic acid (4-hydroxyphenyl) amide (219 mg, 1.00 mmol) and 1-methyl-3-(methyl-phenyl--carbamoyl)-3*H*-imidazol-1-ium iodide (343 mg, 1.00 mmol). HPLC-MS *m/z* = 353 (M+1); *R*<sub>t</sub> = 4.23 min.

20 <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 1.27 (m, 3H), 1.52 (m, 2H), 1.70 (m, 1H), 1.76-1.97 (m, 4H), 2.20 (m, 1H), 3.42 (s, 3H), 7.01 (d, 2H), 7.18 (d, 2H), 7.32-7.50 (m, 7H).

**Example 35** (General procedure 3)

Methyl-phenyl-carbamic acid 4-(2-cyclohexyl-acetyl-amino)-phenyl ester

25

The title compound (284 mg, 77% yield, white crystals) was prepared from 2-cyclohexyl-*N*-(4-hydroxy-phenyl)-acetamide (233 mg, 1.00 mmol) and 1-methyl-3-(methyl-phenyl--carbamoyl)-3*H*-imidazol-1-ium iodide (343 mg, 1.00 mmol). HPLC-MS *m/z* = 367 (M+1); *R*<sub>t</sub> = 4.51 min

30 <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 0.87-1.03 (m, 2H), 1.07-1.38 (m, 3H), 1.60-1.92 (m, 6H), 2.14 (d, 2H), 3.41 (s, 3H), 6.97 (d, 2H), 7.26 (m, 1H), 7.30-7.44 (m, 6H), 7.55 (br.s, 1H, NH);.

**Example 36** (General procedure 3)

*cis/trans*-Methyl-phenyl-carbamic acid 4-[(4-*tert*-butyl-cyclohexanecarbonyl)-amino]-phenyl ester

35

The title compound (353 mg, 86% yield, white crystals) was prepared from *cis/trans*-4-*tert*-butyl-cyclohexanecarboxylic acid (4-hydroxy-phenyl)-amide (275 mg, 1.00 mmol) and 1-methyl-3-(methyl-phenyl-carbamoyl)-3*H*-imidazol-1-ium iodide (343 mg, 1.00 mmol). HPLC-

5 MS *m/z* = 409 (*M*+1); *R*<sub>t</sub> = 5.28 and 5.42 min.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 0.82 + 0.86 (2 x s, 9H), 1.03 (m, 2H), 1.23-1.70 (m, 4H), 1.82-2.22 + 2.58 (m, 4H), 3.42 (s, 3H), 7.01 (m, 2H), 7.26 (m, 1H), 7.31-7.48 (m, 7H, arom. + NH).

**Example 37** (General procedure 3)

10 *trans*-Methyl-phenyl-carbamic acid 4-[(4-*tert*-butyl-cyclohexanecarbonyl)-amino]-phenyl ester

The title compound was obtained from *cis/trans*-4-*tert*-butyl-cyclohexanecarboxylic acid (4-hydroxy-phenyl)-amide by preparative HPLC (method B). *R*<sub>t</sub> = 5.50 min.

15 <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 0.85 (s, 9H), 1.03 (m, 3H), 1.52 (m, 2H), 1.88 (m, 2H), 2.01 (m, 2H), 2.12 (tt, *J* = 12.1, 3.3 Hz, 1H), 3.41 (s, 3H), 7.01 (br.d, 2H), 7.26 (m, 1H), 7.31-7.48 (m, 7H, arom. + NH).

**Example 38** (General procedure 3)

*cis*-Methyl-phenyl-carbamic acid 4-[(4-*tert*-butyl-cyclohexanecarbonyl)-amino]-phenyl ester

20

The title compound was obtained from *cis/trans*-4-*tert*-butyl-cyclohexanecarboxylic acid (4-hydroxy-phenyl)-amide by preparative HPLC (method B). *R*<sub>t</sub> = 6.34 min.

**Example 39** (General procedure 3)

25 Methyl-phenyl-carbamic acid 4-(3,3-dimethyl-butyrylamino)-phenyl ester

The title compound (262 mg, 77% yield) was prepared from *N*-(4-hydroxyphenyl)-3,3-dimethyl-butyramide (275 mg, 1.00 mmol) and 1-methyl-3-(methyl-phenyl-carbamoyl)-3*H*-imidazol-1-ium iodide (343 mg, 1.00 mmol). HPLC-MS *m/z* = 341 (*M*+1); *R*<sub>t</sub> = 4.15 min.

30 <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 1.07 (s, 9H), 2.16 (s, 2H), 3.43 (s, 3H), 6.98 (d, 2H), 7.26 (m, 1H), 7.32-7.43 (m, 6H), 7.51 (br.s, 1H, NH).

**Example 40** (General procedure 3)

Methyl-phenyl-carbamic acid 3-(benzyl)-4-methyl-2-oxo-2*H*-chromen-7-yl ester

35



The title compound was prepared from 3-benzyl-7-hydroxy-4-methyl-2H-chromen-2-one and 3-(methyl-phenyl-carbamoyl)-1-methyl-3H-imidazol-1-ium iodide. HPLC-MS  $m/z$  = 400 (M+1), Rt: 4.90 min.

5 **Example 41** (General procedure 3)

Methyl-phenyl-carbamic acid 3-(3,4-dichloro-benzyl)-4-methyl-2-oxo-2H-chromen-7-yl ester

The title compound was prepared from 3-(3,4-dichloro-benzyl)-7-hydroxy-4-methyl-2H-chromen-2-one and 3-(methyl-phenyl-carbamoyl)-1-methyl-3H-imidazol-1-ium iodide (white  
10 solid). HPLC-MS  $m/z$  = 468 (M+1), Rt: 5.47 min.

**Example 42** (General procedure 3)

Methyl-phenyl-carbamic acid 3-(2-chloro-6-fluoro-benzyl)-4-methyl-2-oxo-2H-chromen-7-yl  
15 ester

The title compound was prepared from 3-(2-chloro-6-fluoro-benzyl)-7-hydroxy-4-methyl-2H-chromen-2-one and 3-(methyl-phenyl-carbamoyl)-1-methyl-3H-imidazol-1-ium iodide by applying procedure 3. HPLC-MS  $m/z$  = 452 (M+1), Rt: 5.15 min.

20 **Example 43** (General procedure 3)

Methyl-phenyl-carbamic acid 3-(2,6-dichloro-benzyl)-4-methyl-2-oxo-2H-chromen-7-yl ester

The title compound was prepared from 3-(2,6-dichloro-benzyl)-7-hydroxy-4-methyl-2H-chromen-2-one and 3-(methyl-phenyl-carbamoyl)-1-methyl-3H-imidazol-1-ium iodide. HPLC-  
25 MS  $m/z$  = 468 (M+1), Rt: 5.37 min.

**Example 44** (General procedure 3)

Methyl-phenyl-carbamic acid 3-(2,6-dichloro-benzyl)-6-chloro-4-methyl-2-oxo-2H-chromen-7-yl ester  
30

The title compound was prepared from 3-(2,6-dichloro-benzyl)-6-chloro-7-hydroxy-4-methyl-2H-chromen-2-one and 3-(methyl-phenyl-carbamoyl)-1-methyl-3H-imidazol-1-ium iodide. HPLC-MS  $m/z$  = 502 (M+1), Rt: 5.68 min.

35 **Example 45** (General procedure 3)

Methyl-phenyl-carbamic acid 6-chloro-3-(2-chloro-6-fluoro-benzyl)-4-n-propyl-2-oxo-2H-chromen-7-yl ester

The title compound was prepared from 3-(4-fluoro-benzyl)-6-chloro-7-hydroxy-4-n-propyl-2H-chromen-2-one and 3-(methyl-phenyl-carbamoyl)-1-methyl-3H-imidazol-1-ium iodide. HPLC-MS  $m/z$  = 480 (M+1),  $R_t$ : 5.61 min.

**Example 46** (General procedure 3)

Methyl-phenyl-carbamic acid 3-(4-methoxy-phenyl)-4-methyl-2-oxo-2H-chromen-7-yl ester

The title compound (90 mg, 43% yield, white solid) was prepared from 7-hydroxy-3-(4-methoxy-phenyl)-4-methyl-chromen-2-one (141 mg, 0.50 mmol) and 1-methyl-3-(methyl-phenyl-carbamoyl)-3H-imidazol-1-ium iodide (175 mg, 0.51 mmol).

$^1\text{H}$  NMR (300MHz, DMSO- $d_6$ ):  $\delta$  2.28 (s, 3H), 3.38 (s, 3H), 3.80 (s, 3H), 7.00 (d, 2H), 7.18-7.33 (m, 5H), 7.40-7.53 (m, 4H), 7.83 (d, 1H); HPLC-MS:  $m/z$  = 416 (M+1);  $R_t$  = 4.67 min.

**Example 47** (General procedure 3)

Methyl-phenyl-carbamic acid 4-methyl-2-oxo-3-phenyl-2H-chromen-7-yl ester

The title compound (120 mg, 52% yield, white solid) was prepared from 7-hydroxy-4-methyl-3-phenyl-chromen-2-one (126 mg, 0.50 mmol) and 1-methyl-3-(methyl-phenyl-carbamoyl)-3H-imidazol-1-ium iodide (175 mg, 0.51 mmol).

$^1\text{H}$  NMR (300MHz, DMSO- $d_6$ ):  $\delta$  2.26 (s, 3H), 3.37 (s, 3H), 7.16-7.54 (m, 12H), 7.86 (d, 1H);

HPLC-MS:  $m/z$  = 386 (M+1);  $R_t$  = 4.69 min.

**Example 48** (General procedure 3)

Methyl-phenyl-carbamic acid 3-(2,5-dimethoxy-phenyl)-4-methyl-2-oxo-2H-chromen-7-yl ester

The title compound (30 mg, 13% yield, white solid) was prepared from 3-(2,5-dimethoxy-phenyl)-7-hydroxy-4-methyl-chromen-2-one (156 mg, 0.50 mmol) and 1-methyl-3-(methyl-phenyl-carbamoyl)-3H-imidazol-1-ium iodide (175 mg, 0.51 mmol).

$^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ ):  $\delta$  2.21 (s, 3H), 3.45 (br.s, 3H), 3.72 (s, 3H), 3.79 (s, 3H), 6.74 (m, 1H), 6.92 (m, 2H), 7.12 (br.s, 2H), 7.26-7.46 (m, 5H), 7.63 (d, 1H); HPLC-MS:  $m/z$  = 446

(M+1);  $R_t$  = 4.60 min.

**Example 49** (General procedure 3)

Methyl-phenyl-carbamic acid 3-(3,4-dimethoxy-phenyl)-4-methyl-2-oxo-2*H*-chromen-7-yl ester.

The title compound (30 mg, 13% yield, oil) was prepared from 3-(3,4-dimethoxy-phenyl)-7-hydroxy-4-methyl-chromen-2-one (156 mg, 0.50 mmol) and 1-methyl-3-(methyl-phenyl-carbamoyl)-3*H*-imidazol-1-ium iodide (175 mg, 0.51 mmol).

$^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ ):  $\delta$  2.31 (s, 3H), 3.45 (br.s, 3H), 3.89 (s, 3H), 4.02 (s, 3H), 6.83 (m, 2H), 6.94 (d, 1H), 7.12 (br.s, 2H), 7.27-7.48 (m, 5H), 7.62 (d, 1H); HPLC-MS:  $m/z$  = 446 (M+1);  $R_t$  = 4.61 min.

**Example 50** (General procedure 2)

4-Chlor-phenyl-methyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 3[(4-chlorophenyl)-methyl-carbamoyl]-1-methyl-3*H*-imidazol-1-ium iodide. The crude product was subjected to flash chromatography (ethyl acetate/heptan, 1:5) (77%, white crystals). HPLC-MS  $m/z$  = 423.1 (M+1),  $R_t$ : 5.3 min.

$\delta_{\text{H}}$ (300MHz;  $\text{CDCl}_3$ ): 3.42 (s, 3H), 6.99 (d, 1H, J 8.7), 7.10-7.20 (m, 4H), 7.30 (d, 2H, J 8.3), 7.37 (d, 2H, J 8.6), 7.88 (dd, 1H, J 8.7 and 2.2), 8.42 bs, 1H).

**Example 51** (General procedure 2)

4-Chlor-phenyl-methyl-carbamic acid 4-(3,5-dichloro-pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(3,5-dichloro-pyridin-2-yloxy)-phenol and 3-[(4-chlorophenyl)-methyl-carbamoyl]-1-methyl-3*H*-imidazol-1-ium iodide. The crude product was subjected to flash chromatography (Quad flash 12, dichlormethane (67%). HPLC-MS  $m/z$  = 422.9 (M+1),  $R_t$ : 5.5 min.

$\delta_{\text{H}}$ (300MHz;  $\text{CDCl}_3$ ): 3.41 (s, 3H), 7.20-7.08 (m, 4H), 7.29 (d, 2H, J 9), 7.37 (dd, 2H, J 6.4 and 2.2), 7.76 (d, 1H, J 2.3), 7.93 (d, 1H, J 2.3).

**Example 52** (General procedure 2)

(4-Chloro-phenyl)-methyl-carbamic acid 4-(2-cyano-5-trifluoromethyl-pyridin-3-yloxy)-phenyl

ester

The title compound was prepared from 4-(2-cyano-5-trifluoromethyl-pyridin-3-yloxy)-phenol and 3-[(4-chlorophenyl)-methyl-carbamoyl]-1-methyl-3H-imidazol-1-ium iodide. The crude product was purified by preparative HPLC (25%). HPLC-MS  $m/z$  = 448.2 ( $M+1$ ), Rt: 5.1 min.  $\delta_H$ (300MHz;  $CDCl_3$ ): 3.43 (s, 3H), 7.12 (d, 2H, J 9.0), 7.19-7.35 (m, 4H), 7.39 (dd, 2H, J 6.6 and 1.8), 7.36-7.41 (m, 1H), 8.63 (d, 1H, J 0.7).

**Example 53** (General procedure 1)

10 Ethyl-phenyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(4-trifluoromethyl-pyridin-2-yloxy)-phenol and *N*-ethyl-*N*-phenylcarbonyl chloride. The crude product was subjected to flash chromatography (ethyl acetate/heptane, 1:5) (78%, white crystals). HPLC-MS  $m/z$  = 403.2 ( $M+1$ ), Rt: 5.17 min.  $\delta_H$ (300MHz;  $CDCl_3$ ): 1.25 (t, 3H, J 6.8), 3.83 (q, 2H, J 6.8), 6.98 (d, 1H, J 8.6), 7.12 (m, 4H), 7.32 (d, 2H, J 7.1), 7.32 (m, 1H), 7.41 (t, 2H, J 7.5), 7.87 (dt, 1H, J 8.7 and 2.7), 8.42 (bs, 1H).

20 **Example 54** (General procedure 1)

Ethyl-phenyl-carbamic acid 4-(4-trifluoromethyl-phenoxy)-phenyl ester

The title compound was prepared from 4-(4-trifluoromethyl-phenoxy)-phenol and *N*-ethyl-*N*-phenylcarbonyl chloride. The crude product was subjected to flash chromatography (ethyl acetate/heptane, 1:5) (77%, white crystals. HPLC-MS  $m/z$  = 402.1 ( $M+1$ ), Rt: 5.6 min.  $\delta_H$ (300MHz;  $CDCl_3$ ): 1.25 (t, 3H, J 7.2), 3.83 (q, 2H, J 7.2), 7.01 (d, 4H, J 8.6) 7.12 (d, 2H, J 8.3), 7.30 (t, 2H, J 6.8), 7.30 (m, 1H), 7.42 (dt, 2H, J 7.5), 7.54 (d, 2H, J 8.6)

**Example 55** (General procedure 2)

30 Benzyl-methyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 3-(benzyl-methyl-carbamoyl)-1-methyl-3H-imidazol-1-ium iodide. The crude product was subjected to flash chromatography (ethyl acetate/heptane, (1:5) (69%, colourless oil) HPLC-MS  $m/z$  = 403.2 ( $M+1$ ), Rt: 5.11min

$\delta_H$ (300MHz;  $CDCl_3$ ): 3.03 (d, 3H, J 8.0), 4.64 (d, 2H, J 24.9), 7.00 (d, 1H), 7.10-7.26 (m, 4H), 7.30-7.50 (m, 5H), 7.88 (dd, 1H), 8.43 (s, 1H).

**Example 56** (General procedure 2)

5 Benzyl-methyl-carbamic acid 4-(3,5-dichloro pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(3,5-dichloro pyridin-2-yloxy)-phenol and 3-(benzyl-methyl-carbamoyl)-1-methyl-3H-imidazol-1-ium iodide.

The crude product was subjected to flash chromatography (Quad flash 12, dichloromethane)  
10 (92%, oil). HPLC-MS  $m/z$  = 403.2 (M+1), Rt: 5.4 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 3.02 (d, 3H, J 7.2), 4.60 (d, 2H, J 24.1), 7.05-7.25 (m, 4H), 7.28-7.45 (m, 5H), 7.76 (d, 1H, J 2.3) 7.95 (d, 1H, J 2.2).

**Example 57** (General procedure 2)

15 tert-Butyl-methyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 3-(tert-Butyl-methyl-carbamoyl)-1-methyl-3H-imidazol-1-ium iodide. The crude product was subjected to preparative HPLC (34%, white crystals). HPLC-MS  $m/z$  = 369.1 (M+1), Rt: 5.17  
20 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 1.47 (s, 9H), 3.08 (s, 3H), 6.99 (d, 1H), 7.09-7.20 (m, 4H), 7.87 (dd, 1H), 8.43 (bs, 1H).

**Example 58** (General procedure 2)

25 Isopropyl-methyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 3-(isopropyl-methyl-carbamoyl)-1-methyl-3H-imidazol-1-ium iodide. The crude product was subjected to flash chromatography (ethyl acetate/heptane 1:5) (77%, white crystals). HPLC-  
30 MS  $m/z$  = 355.1 (M+1), Rt: 4.80 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 1.21 (m, 6H), 2.91 (d, 3H), 4.49 (qi, 1H), 6.99 (d, 1H), 7.10-7.25 (m, 4H) 7.88 (dd, 1H), 8.44 (s, 1H).

**Example 59** (General procedure 2)

35 Cyclohexyl-methyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester.

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 3-(cyclohexyl-methyl-carbamoyl)-1-methyl-3H-imidazol-1-ium iodide. The crude product was subjected to flash chromatography (ethyl acetate/heptane, 1:5) (80%, white crystals). HPLC-MS  $m/z$  = 395.2 (M+1), Rt: 5.7 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 1.13 (m, 1H), 1.50-1.30 (m, 4H), 1.68 (d, 1H, J 13.2), 1.75-1.95 (m, 4H), 2.93 (d, 2H, J 12.1), 2.90-3.00 (m, 1H), 4.02 (t, 1H, J 12.1), 6.99 (d, 1H, J 8.7), 7.10-7.17 (, 4H), 7.88 (dd, 1H, J 8.7 and 2.3), 8.44 (s, 1H).

**Example 60** (General procedure 1)

Dimethyl-carbamic acid 4-(3,5-dichloro pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(3,5-dichloro pyridin-2-yloxy)-phenol and dimethyl-carbamoyl chloride. The crude product was purified by preparative HPLC (38%). HPLC-MS  $m/z$  = 327.0 (M+1), Rt: 4.7 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 2.92 (s, 3H), 3.05 (s, 3H), 7.10-7.25 (m, 4H), 8.17 (d, 1H), 8.34 (d, 1H).

**Example 61** (General procedure 1)

Pyrrolidine-1-carboxylic acid 4-(3,5-dichloro-pyridin-2-yloxy)-phenyl ester

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The title compound was prepared from 4-(3,5-dichloro-pyridine-2-yloxy)-phenol and 1-pyrrolidinecarbamoyl chloride. The crude product was purified by preparative HPLC (64%, white crystals). HPLC-MS  $m/z$  = 353.0 (M+1), Rt: 5.00 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 1.95 (qi, 4H, J 6.4), 3.48 (t, 2H, J 6.4), 3.56 (t, 2H, 6.4), 7.10 (t, 1H, J 2.7), 7.13 (t, 1H, J 2.7), 7.17 (t, 1H, J 2.0), 7.20 (t, 1H, J 2.3), 7.76 (d, 1H, J 2.6), 7.95 (d, 1H J, 2.6).

25

**Example 62** (General procedure 2)

2,3-Dihydro-indole-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester.

30

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 3-(2,3-dihydro-indole-1-carbonyl)-1-methyl-3H-imidazol-1-ium iodide. The crude product was subjected to column chromatography (ethyl acetate/heptane, 1:5) (73%, crystals. HPLC-MS  $m/z$  = 401.1) (M+1), Rt: 5.5 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 3.24 (t, 2H, J 8.4), 4.25 (t, 2H, J 8.4), 7.10 (m, 2H), 7.15-7.35 (m, 6H),

35

7.90 (dd, 2H, J 8.7 and 2.6), 8.44 (bs, 1H).

**Example 63** (General procedure 2)

1,3-Dihydro-isoindole-2-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester.

5

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 3-(1,3-dihydro-isoindole-2-carbonyl)-1-methyl-3H-imidazol-1-ium iodide. The crude product was recrystallized (ethanol) ( $\approx 100$ ). HPLC-MS  $m/z = 401.1$  ( $M+1$ ), Rt: 5.1 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 4.85 (s, 2H), 4.95 (s, 2H), 7.01(d, 1H, J 8.69), 7.16 ( dt, 2H, J 9.4 and  
10 2.7), 7.22-7.29 (m, 2H), 7.30-7.35 (m, 4H), 7.89 (dd, 1H, J 8.6 and 3.0), 8.45 (m, 1H).

**Example 64** (General procedure 2)

Piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

15 The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 1-methyl-3-(piperidine-1-carbonyl)-3H-imidazol-1-ium iodide. The crude product was recrystallized (ethanol) (45%). HPLC-MS  $m/z = 367.02$  ( $M+1$ ), Rt: 4.9 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 1.65 (bs, 6H), 3.58 (d, 4H, J 21.4), 6.99 (d, 1H, J 8.7), 7.10-7.24 (m, 4H), 7.88 (dd, 1H, J 8.7 and 2.2), 8.44 (bs, 1H).

20

**Example 65** (General procedure 2)

2-Methyl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 1-  
25 methyl-3-(2-methyl-piperidine-1-carbonyl)-3H-imidazol-1-ium iodide. The crude product was purified by flash chromatography using a Quad flash 25 (ethyl acetate/heptane (1:6), (71%, white crystals). HPLC-MS  $m/z = 381.1$  ( $M+1$ ), Rt: 5.2 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 1.26 (d, 3H), 1.40-1.85 (m, 6H), 3.03 (t, 1H), 4.11 (dd, 1H), 4.50-4.65  
(m, 1H), 6.95-7.02 (d, 1H), 7.10-7.20 m, 4H), 7.88 (dd, 1H), 8.43 (bs, 1H).

30

**Example 66** (General procedure 2)

3-Methyl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 1-  
35 methyl-3-(3-methyl-piperidine-1-carbonyl)-3H-imidazol-1-ium iodide. The crude product was

purified by flash chromatography using a Quad flash 25 (ethyl acetate/heptane (1:6), (75%, white crystals). HPLC-MS  $m/z$  = 381.1 ( $M+1$ ), Rt: 5.4 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 0.94 (d, 3H), 1.05-1.20 (m, 1H), 1.50-1.80 (m, 3H), 1.80-1.95 (m, 1H), 2.45-2.75 (dt, 1H), 2.80-3.00 (m, 1H), 4.00-4.25 (m, 2H), 6.95-7.05 (d, 1H), 7.10-7.25 (m, 4H), 7.88 (dd, 1H), 8.43 (bs, 1H).

**Example 67** (General procedure 2)

4-Methyl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 1-methyl-3-(4-methyl-piperidine-1-carbonyl)-3H-imidazol-1-ium iodide. The crude product was purified by flash chromatography using a Quad flash 25 (ethyl acetate/heptane (1:6), (73%, white crystals). HPLC-MS  $m/z$  = 381.1 ( $M+1$ ), Rt: 5.4 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 1.00 (d, 3H), 1.23 (dq, 2H), 1.52-1.65 (m, 1H), 1.70 (d, 2H), 2.75-3.05 (m, 2H), 4.15-4.35 (m, 2H), 6.99 (d, 1H), 7.05-7.20 (m, 4H), 7.88 (dd, 1H), 8.43 (s, 1H).

**Example 68** (General procedure 2)

4-Benzyl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 1-methyl-3-(4-benzyl-piperidine-1-carbonyl)-3H-imidazol-1-ium iodide. The crude product was purified by flash chromatography using a Quad flash 25 (ethyl acetate/heptane (1:6), (72%, white crystals). HPLC-MS  $m/z$  = 457.2 ( $M+1$ ), Rt: 6.0 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 1.20-1.40 (m, 2H), 1.65-1.85 (m, 3H), 2.59 (d, 2H), 2.70-3.00 (m, 2H), 4.15-4.35 (m, 2H), 6.99 (d, 1H), 7.05-7.22 (m, 6H), 7.22-7.35 (m, 3H), 7.88 (dd, 1H), 8.43 (bs, 1H).

**Example 69** (General procedure 2)

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 3-(3,4-dihydro-1H-isoquinoline-2-carbonyl)-1-methyl-3H-imidazol-1-ium iodide. The crude product was recrystallized (ethanol) (53%). HPLC-MS  $m/z$  = 415.2 ( $M+1$ ), Rt: 5.3 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 2.96 (d, 2H, J 4.9), 3.86 (dt, 2H, J 23.3 and 6.0), 4.79 (d, 2H, J 35.4),



7.00 (d, 1H, J 8.7), 7.10-7.23 (m, 8H), 7.88 (dt, 1H, J 8.7 and 2.1), 8.44 (s, 1H).

**Example 70** (General procedure 2)

3,4-Dihydro-2H-quinoline-1-carboxylic acid 4-(3,5-dichloro-pyridin-2-yloxy)-phenyl ester

5

The title compound was prepared from 4-(3,5-dichloro-pyridin-2-yloxy)-phenol and 3-(3,4-dihydro-2H-quinoline-1-carbonyl)-1-methyl-3H-imidazol-1-ium iodide. The crude product was recrystallized (ethanol) (68%). HPLC-MS  $m/z$  = 415.2 (M+1), Rt: 5.6 min.

10  $\delta_H$ (300MHz;  $CDCl_3$ ): 2.05 (Qi, 2H, J 6.8), 2.85 (t, 2H, J 6.8), 3.92 (t, 2H, J 6.8), 7.06 (dt, (1H, J 7.4 and 1.1), 7.11-7.19 (m, 4H), 7.21 (t, 1H, J 2.8), 7.24 (t, 1H, J 2.7), 7.77 (d, 1H, J 2.3), 7.75-7.80 (m, 1H), 7.95 (d, 1H, J 2.39).

**Example 71** (General procedure 2)

15 3,4-Dihydro-2H-quinoline-1-carboxylic acid 4-(2-cyano-5-trifluoromethyl-pyridin-3-yloxy)-phenyl ester

The title compound was prepared from 4-(2-cyano-5-trifluoromethyl-pyridin-3-yloxy)-phenol and 3-(3,4-dihydro-2H-quinoline-1-carbonyl)-1-methyl-3H-imidazol-1-ium iodide. The crude product was subjected to flash chromatography (Quad flash 12, dichlormethane) (43%, oil).

20 HPLC-MS  $m/z$  = 440.2 (M+1), Rt: 5.2 min.

$\delta_H$ (300MHz;  $CDCl_3$ ): 2.07 (Qi, 2H, J 6.4), 2.87 (t, 2H, J 6.4), 3.94 (t, 2H, J 6.4), 7.25-7.04 m, 5H), 7.26-7.7.36 (m, 2H), 7.44 (d, 1H, J 1.5), 7.76 (bd, 1H, J 7.2), 8.64 (s, 1H).

**Example 72** (General procedure 3)

25 3,4-Dihydro-2H-quinoline-1-carboxylic acid 3-(3,4-dichloro-benzyl)-4-methyl-2-oxo-2H-chromen-7-yl ester

The title compound was prepared from 3-(3,4-dichloro-benzyl)-7-hydroxy-4-methyl-2H-chromen-2-one and 3-(3,4-dihydro-2H-quinoline-1-carbonyl)-1-methyl-3H-imidazol-1-ium io-  
30 dide. HPLC-MS  $m/z$  = 494 (M+1), Rt: 5.86 min.

**Example 73** (General procedure 3)

3,4-Dihydro-2H-quinoline-1-carboxylic acid 3-benzyl-4-methyl-2-oxo-2H-chromen-7-yl ester

35 The title compound was prepared from 3-benzyl-7-hydroxy-4-methyl-2H-chromen-2-one and

3-(3,4-dihydro-2H-quinoline-1-carbonyl)-1-methyl-3H-imidazol-1-ium iodide. HPLC-MS  $m/z$  = 426 ( $M+1$ ), Rt: 5.34 min.

**Example 74** (General procedure 3)

5 3,4-Dihydro-2H-quinoline-1-carboxylic acid 3-(2-chloro-6-fluoro-benzyl)-4-methyl-2-oxo-2H-chromen-7-yl ester

The title compound was prepared from 3-(2-chloro-6-fluoro-benzyl)-7-hydroxy-4-methyl-2H-chromen-2-one and 3-(3,4-dihydro-2H-quinoline-1-carbonyl)-1-methyl-3H-imidazol-1-ium iodide. HPLC-MS  $m/z$  = 478 ( $M+1$ ), Rt: 5.58 min.

**Example 75** (General procedure 3)

15 3,4-Dihydro-2H-quinoline-1-carboxylic acid 3-(2,6-dichloro-benzyl)-4-methyl-2-oxo-2H-chromen-7-yl ester

The title compound was prepared from 3-(2,6-dichloro-benzyl)-7-hydroxy-4-methyl-2H-chromen-2-one and 3-(3,4-dihydro-2H-quinoline-1-carbonyl)-1-methyl-3H-imidazol-1-ium iodide. HPLC-MS  $m/z$  = 494 ( $M+1$ ), Rt: 5.79 min.

20 **Example 76** (General procedure 3)

3,4-Dihydro-2H-quinoline-1-carboxylic acid 3-(2,6-dichloro-benzyl)-6-chloro-4-methyl-2-oxo-2H-chromen-7-yl ester

The title compound was prepared from 3-(2,6-dichloro-benzyl)-6-chloro-7-hydroxy-4-methyl-2H-chromen-2-one and 3-(3,4-dihydro-2H-quinoline-1-carbonyl)-1-methyl-3H-imidazol-1-ium iodide. HPLC-MS  $m/z$  = 530 ( $M+1$ ), Rt: 6.09 min.

**Example 77** (General procedure 3)

30 3,4-Dihydro-2H-quinoline-1-carboxylic acid 3-(4-fluoro-benzyl)-4-methyl-2-oxo-2H-chromen-7-yl ester

The title compound was prepared from 3-(4-fluoro-benzyl)-7-hydroxy-4-methyl-2H-chromen-2-one and 3-(3,4-dihydro-2H-quinoline-1-carbonyl)-1-methyl-3H-imidazol-1-ium iodide. HPLC-MS  $m/z$  = 444 ( $M+1$ ), Rt: 5.36 min.

**Example 78** (General procedure 3)

3,4-Dihydro-2H-quinoline-1-carboxylic acid 6-chloro-3-(2-chloro-6-fluoro-benzyl)-4-n-propyl-2-oxo-2H-chromen-7-yl ester

- 5 The title compound was prepared from 3-(4-fluoro-benzyl)-6-chloro-7-hydroxy-4-n-propyl-2H-chromen-2-one and 3-(3,4-dihydro-2H-quinoline-1-carbonyl)-1-methyl-3H-imidazol-1-ium iodide. HPLC-MS  $m/z$  = 506 ( $M+1$ ),  $R_t$ : 6.01 min.

**Example 79** (General procedure 3)

- 10 3,4-Dihydro-2H-quinoline-1-carboxylic acid 3-(4-methoxy-phenyl)-4-methyl-2-oxo-2H-chromen-7-yl ester

- The title compound (130 mg, 59% yield, white solid) was prepared from 7-hydroxy-3-(4-methoxy-phenyl)-4-methyl-chromen-2-one (141 mg, 0.50 mmol) and 3-(3,4-dihydro-2H-quinoline-1-carbonyl)-1-methyl-3H-imidazol-1-ium iodide (188 mg, 0.51 mmol).

$^1\text{H}$  NMR (300MHz,  $\text{DMSO}-d_6$ ):  $\delta$  2.00 (quintet, 2H), 2.30 (s, 3H), 2.82 (t, 2H), 3.81 (s, 3H), 3.88 (t, 2H), 7.02 (d, 2H), 7.08 (m, 1H), 7.19 (m, 2H), 7.27 (d, 2H), 7.31 (dd, 1H), 7.41 (d, 1H), 7.72 (d, 1H), 7.88 (d, 1H); HPLC-MS:  $m/z$  = 442 ( $M+1$ );  $R_t$  = 5.13 min.

- 20 **Example 80** (General procedure 3)

3,4-Dihydro-2H-quinoline-1-carboxylic acid 4-methyl-2-oxo-3-phenyl-2H-chromen-7-yl ester

- The title compound (150 mg, 73% yield, white solid) was prepared from 7-hydroxy-4-methyl-3-phenyl-chromen-2-one (126 mg, 0.50 mmol) and 3-(3,4-dihydro-2H-quinoline-1-carbonyl)-1-methyl-3H-imidazol-1-ium iodide (188 mg, 0.51 mmol).

$^1\text{H}$  NMR (300MHz,  $\text{DMSO}-d_6$ ):  $\delta$  1.99 (quintet, 2H), 2.28 (s, 3H), 2.82 (t, 2H), 3.88 (t, 2H), 7.08 (m, 1H), 9.19 (m, 2H), 7.33 (m, 3H), 7.46 (m, 4H), 7.74 (d, 1H), 7.90 (d, 1H); HPLC-MS:  $m/z$  = 412 ( $M+1$ );  $R_t$  = 5.14 min.

30

**Example 81** (General procedure 3)

3,4-Dihydro-2H-quinoline-1-carboxylic acid 3-(2,5-dimethoxy-phenyl)-4-methyl-2-oxo-2H-chromen-7-yl ester

- The title compound (50 mg, 21% yield, white solid) was prepared from 3-(2,5-dimethoxy-phenyl)-7-hydroxy-4-methyl-chromen-2-one (156 mg, 0.50 mmol) and 3-(3,4-dihydro-2H-

quinoline-1-carbonyl)-1-methyl-3*H*-imidazol-1-ium iodide (188 mg, 0.51 mmol).

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 2.08 (quintet, 2H), 2.34 (s, 3H), 2.87 (t, 2H), 3.73 (s, 3H), 3.80 (s, 3H), 3.94 (t, 2H), 6.74 (m, 1H), 6.93 (m, 2H), 7.07-7.26 (m, 5H), 7.68 (d, 1H), 7.77 (br.d, 1H); HPLC-MS: *m/z* = 472 (M+1); R<sub>t</sub> = 5.04 min.

5

**Example 82** (General procedure 3)

3,4-Dihydro-2*H*-quinoline-1-carboxylic acid 3-(3,4-dimethoxy-phenyl)-4-methyl-2-oxo-2*H*-chromen-7-yl ester

10 The title compound (50 mg, 21% yield, oil) was prepared from 3-(3,4-dimethoxy-phenyl)-7-hydroxy-4-methyl-chromen-2-one (156 mg, 0.50 mmol) and 3-(3,4-dihydro-2*H*-quinoline-1-carbonyl)-1-methyl-3*H*-imidazol-1-ium iodide (188 mg, 0.51 mmol).

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 2.08 (quintet, 2H), 2.33 (s, 3H), 2.88 (t, 2H), 3.89 (s, 3H), 4.03 (s, 3H), 4.06 (t, 2H), 6.65 (m, 2H), 6.96 (d, 1H), 7.05-7.25 (m, 5H), 7.68 (d, 1H), 7.77 (br.d, 1H); HPLC-MS: *m/z* = 472 (M+1); R<sub>t</sub> = 5.14 min.

15

**Example 83** (General procedure 2)

7-Trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester.

20

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 1-methyl-3-(7-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carbonyl)-3*H*-imidazol-1-ium iodide. The crude product was subjected to preparative HPLC (66 %). HPLC-MS *m/z*: 483.1 (M+1), R<sub>t</sub>: 5.87 min.

25 <sup>1</sup>H(200MHz; CDCl<sub>3</sub>): 2.08 (Qi, 2H), 2.90 (t, 2H), 3.98 (t, 2H), 7.03 (d, 1H), 7.1-7.40 (m, 6H), 7.90 (dd, 1H), 8.18 (s, 1H), 8.44 (d, 1H).

**Example 84** (General procedure 1)

Morpholine-4-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

30

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and morpholine-4-carbonyl chloride. The crude product was purified by preparative HPLC (37%, white crystals). HPLC-MS *m/z* = 369.1 (M+1), R<sub>t</sub>: 4.3 min.

35 <sup>1</sup>H(300MHz; CDCl<sub>3</sub>): 3.59 (bs, 2H), 3.67 (bs, 2H), 3.76 (m, 4H), 7.01 (d, 1H, J 8.7), 7.12-7.18 (m, 2H), 7.16 (d, 2H, J 3.7), 7.90 (dd, 1H, J 8.7 and 2.6), 8.43 (s, 1H).

**Example 85** (General procedure 1)

Morpholine-4-carboxylic acid 4-(3,5-dichloro-pyridin-4-yloxy)-phenyl ester

- 5 The title compound was prepared from 4-(3,5-dichloro-pyridin-4-yloxy)-phenol and morpholine-4-carbonyl chloride. The crude product was purified by preparative HPLC (66%, white crystals. HPLC-MS  $m/z$  = 368.9 (M+1), Rt: 4.0 min.  
 $\delta_H$ (300MHz;  $CDCl_3$ ): 3.57 (bs, 2H), 3.65 (bs, 2H) 3.74 (m, 4H), 6.83 (d, 1H, J 9), 6.83 (m, 1H) 7.08 (d, 1H, J 9), 7.08 (m, 1H), 8.56 (s, 2H).

10

**Example 86** (General procedure 1)

Morpholine-4-carboxylic acid 4-(4-trifluoromethyl-phenoxy)-phenyl ester

- The title compound was prepared from 4-(4-trifluoromethyl-phenoxy)-phenol and morpholine-4-carbonyl chloride. The crude product was purified by preparative HPLC (74%, white crystals). HPLC-MS  $m/z$  = 368.1 (M+1), Rt: 4.85 min.  
 $\delta_H$ (300MHz;  $CDCl_3$ ): 3.59 (bs, 2H), 3.68 (bs, 2H), 3.75 (m, 4H), 7.04 (d, 2H, J 6.4), 7.04 (m, 2H), 7.14 (d, 1 H, J 9), 7.13 (m, 1H), 7.57 (d, 2H, J 8.3).

20 **Example 87** (General procedure 1)

Morpholine-4-carboxylic acid 4-tert-butoxy-phenyl ester

- The title compound was prepared from 4-(tert-butoxy)-phenol and 4-morpholine-carbamoyl chloride. The crude product was recrystallized (ethanol) (69%, crystals); mp: 128.8-129.5°C.  
25 HPLC-MS  $m/z$  = 280.1 (M+1), Rt: 3.6 min.  
 $\delta_H$ (300MHz;  $CDCl_3$ ): 1.33 (s, 9H, ), 3.58 (bs, 2H), 3.66 (bs, 2H), 6.8-7.1 (m, 4H)

**Example 88** (General procedure 1)

Morpholine-4-carboxylic acid 4-(3,5-dichloro-pyridin-2-yloxy)-phenyl ester

30

- The title compound was prepared from 4-(3,5-dichloro-pyridin-2-yloxy)-phenol and morpholine-4-carbonyl chloride. The crude product was purified by preparative HPLC (45%, crystals. HPLC-MS  $m/z$  = 369.1 (M+1), Rt: 4.3 min.

35 **Example 89** (General procedure 1)

Morpholine-4-carboxylic acid 3-(4-fluoro-benzyl)-4-methyl-2-oxo-2H-chromen-7-yl ester

The title compound was prepared from 3-(4-fluorobenzyl)-7-hydroxy-4-methyl-2H-chromen-2-one and morpholine-4-carbonyl chloride. The crude product was recrystallized (ethanol)

5 (78%, crystals). HPLC-MS  $m/z$  = 398.0 (M+1), Rt: 4.3 min.

$\delta_H$ (200MHz; DMSO- $d_6$ ): 2.47 (s, 3H), 3.45 (bs, 2H), 3.56-3.72 (m, 6H), 3.96 (s, 2H), 7.08 (t, 2H), 7.16-7.35 (m, 4H), 7.83 (d, 1H).

**Example 90** (General procedure 1)

10 Morpholine-4-carboxylic acid 4-(5,7-bis-trifluoromethyl-[1,8]naphthypyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(5,7-bis-trifluoromethyl-[1,8]naphthypyridin-2-yloxy)-phenol and morpholine-4-carbonyl chloride. The crude product was tested without purification

15 tion ( $\approx$  100%). HPLC-MS  $m/z$  = 488.0 (M+1), Rt: 5.0 min.

**Example 91** (General procedure 3)

Morpholine-4-carboxylic acid 3-(3,4-dichloro-benzyl)-4-methyl-2-oxo-2H-chromen-7-yl ester

20 The title compound was prepared from 3-(3,4-dichloro-benzyl)-7-hydroxy-4-methyl-2H-chromen-2-one and 3-(morpholine-4-carbonyl)-1-methyl-3H-imidazol-1-ium iodide. HPLC-MS  $m/z$  = 448 (M+1), Rt: 4.73 min.

**Example 92** (General procedure 3)

25 Morpholine-4-carbamic acid 3-(benzyl)-4-methyl-2-oxo-2H-chromen-7-yl ester

The title compound was prepared from 3-(benzyl)-7-hydroxy-4-methyl-2H-chromen-2-one and 1-methyl-3-(morpholine-4-carbonyl)-3H-imidazol-1-ium iodide. HPLC-MS  $m/z$  = 380 (M+1), Rt: 4.05 min.

30

**Example 93** (General procedure 3)

Morpholine-4-carbamic acid 3-(2-chloro-6-fluoro-benzyl)-4-methyl-2-oxo-2H-chromen-7-yl ester

35

The title compound was prepared from 3-(2-chloro-6-fluoro-benzyl)-7-hydroxy-4-methyl-2H-chromen-2-one and 1-methyl-3-(morpholine-4-carbonyl)-3H-imidazol-1-ium iodide. HPLC-MS  $m/z = 432$  (M+1), Rt: 4.36 min.

5 **Example 94** (General procedure 3)

Morpholine-4-carbamic acid 3-(2,6-dichloro-benzyl)-4-methyl-2-oxo-2H-chromen-7-yl ester

The title compound was prepared from 3-(2,6-dichloro-benzyl)-7-hydroxy-4-methyl-2H-chromen-2-one and 1-methyl-3-(morpholine-4-carbonyl)-3H-imidazol-1-ium iodide. HPLC-MS  
10  $m/z = 448$  (M+1), Rt: 4.59 min.

**Example 95** (General procedure 3)

Morpholine-4-carbamic acid 3-(2,6-dichloro-benzyl)-4-methyl-2-oxo-2H-chromen-7-yl ester

15 The title compound was prepared from 3-(2,6-dichloro-benzyl)-6-chloro-7-hydroxy-4-methyl-2H-chromen-2-one and 1-methyl-3-(morpholine-4-carbonyl)-3H-imidazol-1-ium iodide.  
HPLC-MS  $m/z = 484$  (M+1), Rt: 4.99 min.

**Example 96** (General procedure 3)

20 Morpholine-4-carbamic acid 3-(4-fluoro-benzyl)-4-methyl-2-oxo-2H-chromen-7-yl ester

The title compound was prepared from 3-(4-fluoro-benzyl)-7-hydroxy-4-methyl-2H-chromen-2-one and 1-methyl-3-(morpholine-4-carbonyl)-3H-imidazol-1-ium iodide. HPLC-MS  $m/z =$   
25  $398$  (M+1), Rt: 4.12 min.

**Example 97** (General procedure 3)

Morpholine-4-carbamic acid 6-chloro-3-(2,6-dichloro-benzyl)-4-n-propyl-2-oxo-2H-chromen-7-yl ester

30 The title compound was prepared from 3-(4-fluoro-benzyl)-6-chloro-7-hydroxy-4-n-propyl-2H-chromen-2-one and 1-methyl-3-(morpholine-4-carbonyl)-3H-imidazol-1-ium iodide. HPLC-MS  
 $m/z = 460$  (M+1), Rt: 4.90 min.

**Example 98** (General procedure 3)

35 Morpholine-4-carboxylic acid 4-methyl-2-oxo-3-phenyl-2H-chromen-7-yl ester

The title compound (75 mg, 41% yield, crystals) was prepared from 7-hydroxy-4-methyl-3-phenyl-chromen-2-one (126 mg, 0.50 mmol) and 1-methyl-3-(morpholine-4-carbonyl)-3*H*-imidazol-1-ium iodide (165 mg, 0.51 mmol).

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 2.27 (s, 3H), 3.45 (br.s, 2H), 3.62 (br.s, 2H), 3.68 (m, 4H), 7.23 (dd, 1H), 7.32 (m, 3H), 7.43 (m, 3H), 7.87 (d, 1H); HPLC-MS: *m/z* = 366 (M+1); R<sub>t</sub> = 3.79 min.

**Example 99** (General procedure 3)

Morpholine-4-carboxylic acid 3-(4-methoxy-phenyl)-4-methyl-2-oxo-2*H*-chromen-7-yl ester

The title compound (120 mg, 61% yield, crystals) was prepared from 7-hydroxy-3-(4-methoxy-phenyl)-4-methyl-chromen-2-one (141 mg, 0.50 mmol) and 1-methyl-3-(morpholine-4-carbonyl)-3*H*-imidazol-1-ium iodide (165 mg, 0.51 mmol).

<sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>): δ 2.29 (s, 3H), 3.43 (br.s, 2H), 3.61 (br.s, 2H), 3.66 (m, 4H), 3.81 (s, 3H), 7.01 (d, 2H), 7.20-7.30 (m, 4H), 7.84 (d, 1H); HPLC-MS: *m/z* = 396 (M+1); R<sub>t</sub> = 3.80 min.

**Example 100** (General procedure 3)

Morpholine-4-carboxylic acid 3-(3,4-dimethoxy-phenyl)-4-methyl-2-oxo-2*H*-chromen-7-yl ester

The title compound (120 mg, 56% yield) was prepared from 3-(3,4-dimethoxy-phenyl)-7-hydroxy-4-methyl-chromen-2-one (156 mg, 0.50 mmol) and 1-methyl-3-(morpholine-4-carbonyl)-3*H*-imidazol-1-ium iodide (165 mg, 0.51 mmol).

<sup>1</sup>H NMR (300MHz, DMSO-*d*<sub>6</sub>): δ 2.29 (s, 3H), 3.46 (br.s, 2H), 3.62 (br.s, 2H), 3.67 (m, 4H), 3.74 (s, 3H), 3.81 (s, 3H), 6.83 (dd, 1H), 6.92 (d, 1H), 7.02 (d, 1H), 7.22 (dd, 1H), 7.30 (d, 1H), 7.85 (d, 1H); HPLC-MS: *m/z* = 426 (M+1); R<sub>t</sub> = 3.80 min.

**Example 101** (General procedure 3)

Morpholine-4-carboxylic acid 3-(2,5-dimethoxy-phenyl)-4-methyl-2-oxo-2*H*-chromen-7-yl ester



The title compound (120 mg, 56% yield) was prepared from 3-(2,5-dimethoxy-phenyl)-7-hydroxy-4-methyl-chromen-2-one (156 mg, 0.50 mmol) and 1-methyl-3-(morpholine-4-carbonyl)-3H-imidazol-1-ium iodide (165 mg, 0.51 mmol).

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 2.23 (s, 3H), 3.60 (br.s, 2H), 3.74 (br.s, 2H + s, 3H), 3.80 (m, 4H + s, 3H), 6.73 (m, 1H), 6.92 (m, 2H), 7.13 (m, 2H), 7.64 (d, 1H); HPLC-MSA): *m/z* = 426 (M+1); R<sub>t</sub> = 3.69 min.

**Example 102** (General procedure 2)

2.6-dimethyl-morpholine-4-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 3-(2,6-dimethyl-morpholine-4-carbonyl)-1-methyl-3H-imidazol-1-ium iodide. The crude product was purified by preparative HPLC (39%, colorless oil). HPLC-MS *m/z* = 397.1 (M+1), R<sub>t</sub>: 4.64 min.

δ<sub>H</sub>(200MHz; CDCl<sub>3</sub>): 1.22 (s, 3H), 1.25 (s, 3H), 2.50-3.00 (m, 2H), 3.55-3.9 (m, 2H), 4.00-3.30 bd, 2H), 6.90-7.50 (m, 5H), 7.91 (dd, 1H), 8.44 (bs, 1H).

**Example 103**

Dimethylcarbamic acid benzotriazol-1-yl ester

**Example 104**

2-Oxo-*N*-*p*-tolylacetamide O-(cyclohexylcarbamoyl)-oxime

**Example 105**

10,11-Dihydro-dibenzo[a,d]cyclohepten-5-one O-cyclohexylcarbamoyl-oxime

**Example 106**

1-(4-Chlorophenyl)-non-1-en-3-one O-cyclohexylcarbamoyl-oxime

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**Example 107**

1,7,7-Trimethyl-bicyclo[2.2.1]heptan-2-one O-cyclohexylcarbamoyl-oxime

**Example 108**

1-(4-Bromophenyl)-6-methyl-hept-1-en-3-one O-isopropylcarbamoyl-oxime

35

**Example 109**

1-(4-Chloro-phenyl)-non-1-en-3-one O-isopropylcarbamoyl-oxime

**5 Example 110**

4-Bromo-2-(4-chlorobenzyl)-2H-pyrazole-3-carbaldehyde O-methylcarbamoyl-oxime

**Example 111**

1-(4-Bromophenyl)-6-methyl-hept-1-en-3-one O-propylcarbamoyl-oxime

10

**Example 112**

N-(4-Fluorobenzylcarbamoyloxy)-isobutyrimidoyl chloride

**Example 113**

15 N-(2-Hydroxy-2-phenylethylcarbamoyloxy)-isobutyrimidoyl chloride

**Example 114**

Dimethylcarbamic acid 6-methanesulfonyl-indol-1-yl ester

**20 Example 115**

1-Biphenyl-4-yl-3-methylamino-propenone-cyclohexyl-carbamic acid

**Example 116**

Dimethylcarbamic acid 4-oxo-1,2,3-benzotriazin-3-yl ester

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**Example 117**

[1-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-1H-pyrrol-2-yl]-carbamic acid 4-chloro-phenyl ester

**Example 118 (General procedure 6)**

30 N-Methyl-N-phenyl-5-hexylsulfanyl-3-p-tolyl-[1,2,4]triazole-1-carboxamide

The title compound was prepared from p-toluoyl chloride, 1-bromo-hexane and N-methyl-phenyl-carbamoyl chloride. The crude product was recrystallized (ethanol/ water); HPLC-MS  $m/z = 409.2$  (M+1),  $R_t$ : 6.66 min.

35  $\delta_H$  (300MHz; [ $^2H_6$ ]DMSO): 0.87 (t, 3H), 1.20-1.35 (m, 4H), 1.35-1.48 (m, 2H), 1.72 (q, 2H), 2.99 (s, 3H), 3.25 (t, 2H), 3.46 (s, 3H), 7.13-7.30 (m, 5H), 7.36 (t, 2H), 7.52 (d, 2H).

**Example 119** (General procedure 6)

N-Methyl-N-phenethyl-5-ethyl-3-(4-chlorophenyl)-[1,2,4]triazole-1-carboxamide

- 5 The title compound was prepared from 4-chlorobenzoyl chloride, 1-bromo-ethane and N-methyl-phenethyl-carbamoyl chloride. The crude product was subjected to preparative HPLC; HPLC-MS  $m/z = 401.1$  ( $M+1$ ),  $R_t$ : 6.17 min.
- $\delta_H$ (300MHz; [ $^2H_6$ ]DMSO): 1.37 (t, 3H), 2.98 (t, 2H), 3.11 (bs, 3H), 3.23 (Q, 2H), 3.80 (m, 2H), 7.10-7.40 (m, 5H), 7.58 (d, 2H), 8.03 (d, 2H).

10

**Example 120** (General procedure 6)

[3-(4-Chlorophenyl)-5-methylsulfanyl-[1,2,4]triazol-1-yl]-morpholin-4-yl-methanone

- The title compound was prepared from 4-chlorobenzoyl chloride, methyl iodide and morpholine-4-carbonyl chloride. The crude product was used without further purification; HPLC-MS  $m/z = 339.1$  ( $M+1$ ),  $R_t$ : 4.68 min.
- 15  $\delta_H$ (300MHz; [ $^2H_6$ ]DMSO): 2.68 (s, 3H), 3.25-3.65 (m, 4H), 3.65-3.85 (m, 4H), 7.58 (d, 2H), 8.03 (d, 2H).

20 **Example 121** (General procedure 6)

N,N-Dimethyl-5-methylsulfanyl-3-naphthalen-2-yl-[1,2,4]triazole-1-carboxamide

- The title compound was prepared from 2-naphthoyl chloride, methyl iodide and dimethyl carbamoyl chloride. The crude product was recrystallized from ethanol; HPLC-MS  $m/z = 313.2$  ( $M+1$ ),  $R_t$ : 4.91 min.
- 25  $\delta_H$ (300MHz; [ $^2H_6$ ]DMSO): 2.74 (s, 3H), 3.18 (s, 6H), 7.53-7.65 (m, 2H), 7.92-8.00 (m, 1H), 8.00-8.17 (m, 3H), 8.62 (s, 1H).

**Example 122** (General procedure 6)

N,N-Dimethyl-3-(4-chloro-phenyl)-5-ethylsulfanyl-[1,2,4]triazole-1-carboxamide

30

- The title compound was prepared from 2-naphthoyl chloride, methyl iodide and dimethyl carbamoyl chloride. The crude product was recrystallized from ethanol; HPLC-MS  $m/z = 311.0$  ( $M+1$ ),  $R_t$ : 5.13 min.
- $\delta_H$ (300MHz; [ $^2H_6$ ]DMSO): 1.39 (t, 3H), 3.13 (bs, 6H), 3.26 (q, 2H), 7.58 (d, 2H), 8.03 (d, 2H).

35

**Example 123** (General procedure 6)

N,N-Dimethyl-3-biphenyl-4-yl-5-methylsulfanyl-[1,2,4]triazole-1-carboxamide

The title compound was prepared from 3-biphenylcarbonyl chloride, methyl iodide and dimethyl carbamoyl chloride. The crude product was without further purification; HPLC-MS m/z = 339.1 (M+1), R<sub>t</sub>: 5.27 in.

$\delta_H$ (300MHz; [<sup>2</sup>H<sub>6</sub>]DMSO): 2.70 (s, 3H), 3.16 (bs, 6H), 7.40 (t, 1H), 7.50 (t, 2H), 7.73 (d, 2H), 7.82 (d, 2H), 8.12 (d, 2H).

**Example 124**

N,N-Dimethyl-3-(4-chloro-phenyl)-5-methylsulfanyl-[1,2,4]triazole-1-carboxamide

**Example 126**

N-(4-Chlorophenyl)-3-(4-chlorophenyl)-5-(3-hydroxypropyl)-pyrazole-1-carboxamide.

**Example 127**

5-Morpholin-4-yl-3-(4-phenoxyphenyl)-pyrazole-1-carboxylic acid phenethylamide

**Example 128**

N-Phenyl-4-(4-chlorobenzenesulfonyl)-5-(4-chlorophenyl)-pyrazole-1-carboxamide

**Example 129**

N-(3,4-Dichlorophenyl)-2-phenyl-benzimidazole-1-carboxamide

**Example 130**

Dimethyl-carbamic acid 5-isopropylsulfanyl-4-(3-trifluoromethyl-phenyl)-4H-[1,2,4]triazol-3-yl ester

**Example 131**

Dimethyl carbamic acid 1-benzyl-2-oxo-3,5-diphenyl-1,2-dihydro-pyridin-4-yl ester

**Example 132**

Dimethyl-carbamic acid 7-methoxy-1-methyl-2-oxo-1,2-dihydro-quinolin-4-yl ester

**Example 133**

Dimethyl carbamic acid 4-(3-chloro-phenyl)-5-(4-methyl-benzylsulfanyl)-4H-[1,2,4]triazol-3-yl

ester

**Example 134** (General procedure 7)

5 4-Methyl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 1-methylpiperazine. White solid, m.p. 249 - 250 °C (decomp.); HPLC-MS m/z = 458 (M+H), R<sub>t</sub>: 3.15 min.; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 11.56 (br, 1H, NH), 8.61 - 8.54 (br, 1H, py-H6), 8.30 - 8.20 (m, 1H, py-H4), 7.32 - 7.19 (d+ br s, 5H, py-H3 + C<sub>6</sub>H<sub>4</sub>), 4.5 - 3.0 (br, 10H, 8 CH + H<sub>2</sub>O), 2.79 (s, 3H, CH<sub>3</sub>); IR (KBr): ν 1713 (C=O).

**Example 135** (General procedure 7)

15 4-Benzyl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 1-benzylpiperazine. White solid, m.p. 229 - 231 °C; HPLC-MS m/z = 458 (M+H), R<sub>t</sub>: 3.15 min.; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 11.17 (br, 1H, NH), 8.61 - 8.54 (br, 1H, py-H6), 8.30 - 8.20 (m, 1H, py-H4), 7.74 - 7.59 (m, 2H, arom.), 7.52 - 7.41 (m, 3H, arom.), 7.31 - 7.17 (d+ br s, 5H, py-H3 + C<sub>6</sub>H<sub>4</sub>), 4.5 - 4.0 (br, 4H, CH<sub>2</sub> + 2 CH), 3.8 - 3.0 (br, 8H, 6 CH + H<sub>2</sub>O); IR (KBr): ν 1720 (C=O).

**Example 136** (General procedure 7)

25 4-(2-Hydroxyethyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 1-(2-hydroxyethyl)-piperazine. White solid, m.p. 255 °C; HPLC-MS m/z = 412 (M+H), R<sub>t</sub>: 2.12 min.; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 10.66 (br, 1H, NH), 8.61 - 8.54 (br, 1H, py-H6), 8.30 - 8.20 (m, 1H, py-H4), 7.32 - 7.20 (d+ br s, 5H, py-H3 + C<sub>6</sub>H<sub>4</sub>), 5.39 (br, 1H, OH), 4.18 (br, 2H), 3.87 - 3.70 (br t, 2H), 3.70 - 3.02 (br, 8H + water); IR (KBr): ν 1714 (C=O).

**Example 137** (General procedure 7)

35 4-(2-Oxo-2-pyrrolidin-1-yl-ethyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 1-(pyrrolidinocarbonylmethyl)-piperazine. White solid, m.p. 224 °C; HPLC-MS m/z = 479 (M+H), R<sub>t</sub>: 2.73 min.; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 10.43 (br, 1H, NH), 8.62 - 8.52 (br, 1H, py-H6), 8.31 - 8.20 (m, 1H, py-H4), 7.34 - 7.18 (d+ br s, 5H, py-H3 + C<sub>6</sub>H<sub>4</sub>), 4.40 - 3.05 (br, CH<sub>2</sub> at 4.26 + water at 3.37 + N-C-H), 2.03 - 1.72 (m, 4H, CH<sub>2</sub>).

**Example 138** (General procedure 7)

4-Phenyl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 1-phenyl-piperazine (0.5 mmol). The crude product (0.15 g) was partitioned between ethyl acetate (4 ml) and ethyldiisopropylamine (0.04 ml) dissolved in water (4 ml). The organic layer was washed with water (2 x 5 ml), dried over sodium sulfate. The drying agent was filtered off, and the solvent was removed from the filtrate *in vacuo* to give the title compound (0.095 g). White crystals, m.p. 117 °C; HPLC-MS m/z = 444 (M+H), R<sub>t</sub>: 5.12 min.; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.61 - 8.55 (br, 1H, py-H6), 8.29 - 8.20 (m, 1H, py-H4), 7.32 - 7.14 (m, 7H, py-H3 + C<sub>6</sub>H<sub>4</sub> + 2 arom.), 7.05 - 6.71 (m, 3H, arom.), 3.83 - 3.51 (br, 4H, 2 CH<sub>2</sub>), 3.28 - 2.99 (m, 4H, 2 CH<sub>2</sub>).

**Example 139** (General procedure 8)

Methyl-phenyl-carbamic acid pyrazol-1-yl ester

The title compound was prepared from 1-hydroxypyrazole and N-methyl-N-phenylcarbamoil chloride. The crude product was subjected to flash chromatography (Quad flash 25, EtOAc-heptane) (79%, oil which slowly crystallizes). HPLC-MS m/z = 218.1 (M+1), R<sub>t</sub>: 2.82 min. Mp 63-67 °C

δ<sub>H</sub>(300MHz; CDCl<sub>3</sub>): 3.45 (bs, 3H), 6.28 (s, 3H), 7.30-7.47 (m, 7H).

**Example 140** (General procedure 8)

Methyl-phenyl-carbamic acid 4-bromo-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-4-bromopyrazole and N-methyl-N-phenylcarbamoil chloride. The crude product was subjected to flash chromatography (Quad flash 25, EtOAc-heptane) (89%, oil). HPLC-MS m/z = 298.0 (M+1), R<sub>t</sub>: 3.77 min.

δ<sub>H</sub>(300MHz; CDCl<sub>3</sub>): 3.44 (bs, 3H), 7.32-7.47 (m, 7H).

**Example 141** (General procedure 8)

Methyl-phenyl-carbamic acid 3,4,5-tribromo-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-3,4,5-bromopyrazole and N-methyl-N-phenylcarbonyl chloride. The crude product was subjected to flash chromatography (Quad  
5 flash 25, EtOAc-heptane) (93%, colorless crystals). HPLC-MS  $m/z$  = 455.8 (M+1), Rt: 4.88 min. Mp 115-119 °C  
 $\delta_H$ (300MHz;  $CDCl_3$ ): 3.44 (bs, 3H), 7.36-7.48 (m, 5H).

**Example 142** (General procedure 8)

10 Methyl-phenyl-carbamic acid 3-(4-methoxy-phenyl)-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-3-(4-methoxyphenyl)pyrazole and N-methyl-N-phenylcarbonyl chloride. The crude product was subjected to flash chromatography (Quad flash 25, EtOAc-heptane) (93%, oil). HPLC-MS  $m/z$  = 346.1 (M+Na), Rt: 4.21 min.  
 $\delta_H$ (300MHz;  $CDCl_3$ ): 3.45 (bs, 3H), 3.84 (s, 3H), 6.50 (d, 1H), 6.91 (d, 2H), 7.30-7.48 (m, 6H),  
15 7.70 (d, 2H).

**Example 143** (General procedure 8)

Methyl-phenyl-carbamic acid imidazol-1-yl ester

The title compound was prepared from 1-hydroxyimidazole and N-methyl-N-phenylcarbonyl  
20 chloride. The crude product was subjected to flash chromatography (Quad flash 25, EtOAc-heptane) (68%, oil). HPLC-MS  $m/z$  = 218.1 (M+1), Rt: 1.53 min.  
 $\delta_H$ (300MHz;  $CDCl_3$ ): 3.45 (bs, 3H), 7.00 (bs, 1H), 7.05 (bs, 1H), 7.32-7.49 (m, 5H), 7.55 (bs, 1H).

25 **Example 144** (General procedure 8)

Methyl-phenyl-carbamic acid [1,2,3]triazol-1-yl ester

The title compound was prepared from 1-hydroxy-1,2,3-triazole and N-methyl-N-phenylcarbonyl chloride. The crude product was subjected to flash chromatography (Quad  
flash 25, EtOAc-heptane) (80%, oil). HPLC-MS  $m/z$  = 219.1 (M+1), Rt: 2.50 min. Mp 105-106  
30 °C.  
 $\delta_H$ (300MHz;  $CDCl_3$ ): 3.46 (bs, 3H), 7.00 (bs, 1H), 7.05 (bs, 1H), 7.31-7.48 (m, 5H), 7.62 (bs, 1H), 7.74 (s, 1H).

**Example 145** (General procedure 7)

35 4-(Isopropylcarbonyl-methyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-

yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 1-methyl-piperazine. White solid, m.p. 234 - 235 °C; HPLC-MS m/z = 466 (M+H), R<sub>t</sub>: 2.75 min.; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 10.50 (br, 1H, NH), 8.66 - 8.54 (br, 2H, NH + py-H6), 8.30 - 8.20 (dd, 1H, py-H4), 7.31 - 7.20 (d+ br s, 5H, py-H3 + C<sub>6</sub>H<sub>4</sub>), 4.00 - 3.82 (br m, 5H, methin + 4 CH), 3.70 - 3.09 (br, 9H, 6H + water), 1.11 (d, 6H, CH<sub>3</sub>).

**Example 146** (General procedure 9)

4-Cyclopentyl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester.

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-cyclopentyl-piperazine. White solid, m.p. 294 - 295 °C; HPLC-MS m/z = 436 (M+H), R<sub>t</sub>: 2.92 min.; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 11.15 (br, 1H, NH), 8.60 - 8.55 (br, 1H, py-H6), 8.29 - 8.20 (m, 1H, py-H4), 7.32 - 7.21 (d+ br s, 5H, py-H3 + C<sub>6</sub>H<sub>4</sub>), 4.35 - 3.98 (br, 2H), 3.72 - 3.37 (br m, 5H), 3.29 - 2.97 (br, 2H), 2.12 - 1.45 (br m, 8H).

**Example 147** (General procedure 9)

4-Butyl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-butyl-piperazine. White solid, m.p. 221 - 222 °C; HPLC-MS m/z = 424 (M+H), R<sub>t</sub>: 2.94 min.; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 10.86 (br, 1H, NH), 8.60 - 8.55 (br, 1H, py-H6), 8.29 - 8.21 (m, 1H, py-H4), 7.31 - 7.22 (d+ br s, 5H, py-H3 + C<sub>6</sub>H<sub>4</sub>), 4.32 - 4.03 (br, 2H), 3.65 - 3.44 (br m, 4H), 3.28 - 2.97 (br, 4H), 1.81 - 1.60 (br m, 2H), 1.45 - 1.22 (br, 4H), 0.92 (t, 3H, CH<sub>3</sub>).

**Example 148** (General procedure 1)

4-(Methyl-phenyl-carbamoyloxy)-benzoic acid 2,5-dioxo-pyrrolidin-1-yl ester

The title product was prepared from 4-Hydroxy-benzoic acid 2,5-dioxo-pyrrolidin-1-yl ester and N-methyl-N-phenylcarbamoyl chloride. The crude product was recrystallized from



methanol (74%, white crystals).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.13 (d, 2H), 7.38-7.55 (m, 6H), 7.30 (t, 1H), 3.37 (s, 3H), 2.89 (s, 4H).

**Example 149** (General procedure 10)

5 4-Hydroxymethyl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title product was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 4-hydroxymethylpiperidine. The crude product was subjected to flash chromatography (ethyl acetate/heptane, 1:2 → 2:1) (78%, light yellow oil). The purified product was crystallized from ethyl acetate/heptane (51%, white solid). HPLC-MS: *m/z* = 397.1 (M+1); *R<sub>t</sub>*: 4.08 min.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.44 (s, 1H), 7.88 (dd, 1H), 7.17 (d, 2H), 7.13 (d, 2H), 7.00 (d, 2H), 4.45-4.20 (bs, 2H), 3.55 (t, 2H), 3.10-2.75 (m, 2H), 1.95-1.65 (m, 3H), 1.47 (t, 1H), 1.29 (dq, 2H).

15 **Example 150** (General procedure 10)

4-Oxo-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title product was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 4-piperidone monohydrate. The solvent used was a mixture of dichloromethane and dimethylformamide (1:1). The crude product was subjected to preparative HPLC (7%, oil). HPLC-MS: *m/z* = 381.1 (M+1); *R<sub>t</sub>*: 4.17 min.

**Example 151** (General procedure 10)

4-[5-(4-Dimethylamino-phenyl)-1H-pyrazol-3-yl]-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title product was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and N,N-dimethyl-4-[3-(4-piperidinyl)-1H-pyrazol-5-yl]aniline. The solvent used was a mixture of dichloromethane and dimethylformamide (1:2). The crude product was subjected to preparative HPLC (4%, oil). HPLC-MS: *m/z* = 552.2 (M+1); *R<sub>t</sub>*: 4.17 min.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.44 (d, 1H), 7.89 (dd, 1H), 7.53 (d, 2H), 7.22-7.10 (m, 4H), 7.00 (d, 1H), 6.73 (d, 2H), 6.27 (s, 1H), 4.45-4.20 (ds, 2H), 3.25-2.95 (m, 3H), 2.88 (s, 6H), 2.15-2.00 (m, 2H), 1.90-1.70 (dq, 2H).

35 **Example 152** (General procedure 10)

4-(5-Furan-2-yl-1H-pyrazol-3-yl)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title product was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 4-[3-(2-furyl)-1H-pyrazol-5-yl]piperidine. The solvent used was a mixture of dichloromethane and dimethylformamide (1:2). The crude product was subjected to preparative HPLC (4%, oil).

HPLC-MS:  $m/z$  = 499.1 (M+1);  $R_t$ : 4.60 min.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 8.44 (d, 1H), 7.89 (dd, 1H), 7.45 ((dd, 1H), 7.24-7.10 (m, 4H), 6.99 (d, 1H), 6.62 (d, 1H), 6.48 (dd, 1H), 6.34 (s, 1H), 4.40-4.25 (bs, 2H), 3.25-2.85 (m, 3H), 2.08 (d, 2H), 1.79 (dq, 2H).

**Example 153** (General procedure 10)

4-Benzylamino-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title product was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and benzyl-piperidin-4-yl-amine. The crude product was subjected to preparative HPLC (20%, oil).

HPLC-MS:  $m/z$  = 472.2 (M+1);  $R_t$ : 3.34 min.

**Example 154** (General procedure 10)

4-(3,4-Dihydro-1H-isoquinolin-2-ylmethyl)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title product was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 2-Piperidin-4-ylmethyl-1,2,3,4-tetrahydro-isoquinoline. The crude product was subjected to preparative HPLC (12%, oil). HPLC-MS:  $m/z$  = 512.2 (M+1);  $R_t$ : 3.21 min.

**Example 155** (General procedure 1)

Methyl-phenyl-carbamic acid 4-(1,3,5-trimethyl-1H-pyrazol-4-ylmethyl)-phenyl ester

The title product was prepared from 4-[(1,3,5-trimethyl-1H-pyrazol-4-yl)methyl]phenol and N-methyl-N-phenylcarbonyl chloride. The crude product was subjected to preparative HPLC (88%, oil). HPLC-MS:  $m/z$  = 350.0 (M+1);  $R_t$ : 3.52 min. (66% purity).

**Example 156** (General procedure 10)

3-Hydroxymethyl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl es-

ter

The title product was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 3-hydroxymethyl-piperidine. The crude product was subjected to flash chromatography (Quad Flash 12, ethyl acetate/heptane 1:2). (56%, colourless oil). HPLC-MS:  $m/z$  = 397.1 (M+1);  $R_t$ : 4.19 min.

$^1\text{H}$  NMR (DMSO- $d_6$ , 90 °C): 8.37 (s, 1H), 8.00 (dd, 1H), 6.95-7.10 (m, 5H), 4.09 (bs, 1H), 3.91 (dd, 1H), 3.78 (d, 1H), 3.21 (m, 1H), 3.15 (t, 1H), 2.80-2.90 (m, 1H), 2.65 (t, 1H), 1.45-1.70 (m, 3H), 1.25-1.45 (m, 1H), 1.08 (q, 1H).

**Example 157** (General procedure 10)

3-Hydroxy-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title product was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 3-hydroxy-piperidine. The crude product was subjected to flash chromatography (Quad Flash 12, ethyl acetate/heptane (1:2) (56%, colourless oil). HPLC-MS:  $m/z$  = 383.0 (M+1);  $R_t$ : 3.98 min.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 8.43 (s, 1H), 7.89 (dd, 1H), 7.23-7.10 (m, 4H), 7.00 (d, 1H), 3.80-4.00 (m, 2H), 3.60-3.80 (m, 1H), 3.25-3.50 (m, 2H), 1.80-2.05 (m, 2H), 1.50-1.70 (m, 3H).

**Example 158** (General procedure 10)

4-Benzyl-4-hydroxy-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title product was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 4-benzyl-4-hydroxypiperidine. The crude product was subjected to flash chromatography (Quad Flash 12, ethyl acetate/heptane (1:2) (48%, colourless oil). HPLC-MS:  $m/z$  = 473.0 (M+1);  $R_t$ : 5.04 min.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 8.44 (s, 1H), 7.89 (dd, 1H), 7.28-7.45 (m, 3H), 7.10-7.24 (m, 6H), 7.00 (d, 1H), 4.00-4.14 (bs, 2H), 3.15-3.45 (dt, 2H), 2.81 (s, 2H), 1.66-1.85 (dt, 2H), 1.55-1.65 (m, 2H), 1.27 (s, 1H).

**Example 159** (General procedure 1)

Methyl-phenyl-carbamic acid 4-(2-cyano-ethyl)-phenyl ester

The title product was prepared from 3-(4-hydroxyphenyl)proprionitrile and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (11%, colourless oil). HPLC-MS:  $m/z$  = 281.2 (M+1);  $R_t$ : 3.75 min, purity 80%.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.26-7.50 (m, 7H), 7.00-7.15 (m, 2H), 3.42 (s, 3H), 2.94 (t, 2H), 2.59 (t, 2H).

**Example 160** (General procedure 1)

Methyl-phenyl-carbamic acid 4-([1,2,3,4]thiatriazol-5-ylamino)-phenyl ester

The title product was prepared from 4-(1,2,3,4-thiatriazol-5-ylamino)phenol and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC. (10%, light brown solid material). HPLC-MS:  $m/z$  = 328.0 (M+1);  $R_t$ : 3.69 min, purity 81%.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.61 (d, 2H), 7.38-7.52 (m, 4H), 7.19-7.35 (m, 2H), 6.86-6.95 (m, 1H), 3.35 (s, 3H), 3.33 (s, 1H).

**Example 161** (General procedure 1)

Methyl-phenyl-carbamic acid 4-pentyl-phenyl ester

The title product was prepared from 4-pentylphenol and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC. (4%, light brown oil). HPLC-MS:

$m/z$  = 298.2 (M+1);  $R_t$ : 5.61 min.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.31-7.50 (m, 4H), 7.18-7.30 (m, 1H), 7.13 (d, 2H), 7.00 (d, 2H), 3.42 (s, 3H), 2.57 (t, 2H), 1.58 (qi, 2H), 1.20-1.40 (m, 4H), 0.87 (t, 3H).

**Example 162** (General procedure 1)

Methyl-phenyl-carbamic acid 4-(2-methoxy-ethyl)-phenyl ester

The title product was prepared from 4-(2-methoxyethyl)phenol and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC. (4%, light yellow oil). HPLC-MS:  $m/z$  = 286.1 (M+1);  $R_t$ : 4.01 min.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.30-7.48 (m, 4H), 7.12-7.30 (m, 3H), 7.03 (d, 2H), 3.56 (t, 2H), 3.42 (s, 3H), 3.33 (s, 3H), 2.85 (t, 2H).

**Example 163** (General procedure 10)

4-Hydroxy-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title product was prepared from 4-(5-trifluoromethyl-pyridin)-2-yloxy)-phenol and 4-hydroxypiperidine. The crude product was subjected to flash chromatography (ethyl acetate/heptane (1:1) (48%, light yellow oil). HPLC-MS:  $m/z$  = 383.0 (M+1);  $R_t$ : 3.88 min. purity 93%.

5  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 8.44 (s, 1H), 7.89 (dd, 1H), 7.08-7.20 (m, 4H), 6.99 (d, 1H), 3.85-4.10 (m, 3H), 3.20-3.45 (m, 2H), 1.85-2.02 (m, 2H), 1.50-1.70 (m, 3H).

**Example 164** (General procedure 1)

Methyl-phenyl-carbamic acid 4-acetyl-phenyl ester

10

The title product was prepared from 4'-hydroxyacetophenone and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC. (78%, colourless oil). HPLC-MS:  $m/z$  = 270.1 (M+1);  $R_t$ : 3.62 min.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.96 (d, 2H), 7.15-7.7.48 (m, 7 H), 3.43 (s, 3H), 2.58 (s, 3H).

15

**Example 165** (General procedure 1)

Methyl-phenyl-carbamic acid pyridin-4-yl ester

20 The title product was prepared from 4-hydroxypyridine and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC. (11%, yellow solid). HPLC-MS:  $m/z$  = 229.2 (M+1);  $R_t$ : 1.66 min, purity: 67%.

**Example 166** (General procedure 1)

Methyl-phenyl-carbamic acid pyridin-3-yl ester

25

The title product was prepared from 3-hydroxypyridine and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC. (94%, colourless oil).

HPLC-MS:  $m/z$  = 229.2 (M+1);  $R_t$ : 2.54 min.

30  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 10.70 (bs, 1H), 8.50 (d, 1H), 8.45-8.65 (m, 1H), 7.70-7.90 (m, 1H), 7.51 (dd, 1H), 7.42 (d, 2H), 7.34 (d, 2H), 7.28-7.37 (m, 1H), 3.43 (s, 3H).

**Example 167** (General procedure 1)

Methyl-phenyl-carbamic acid 6-methyl-pyridin-3-yl ester

35 The title product was prepared from 3-hydroxy-6-methyl-pyridine and N-methyl-N-

phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC. (79%, colourless oil). HPLC-MS:  $m/z$  = 243.1 (M+1);  $R_f$ : 2.24 min.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 10.8 (bs, 1H), 8.54 (m, 1H), 7.76 (m, 1H), 7.26-7.50 (m, 6H), 3.42 (s, 3H), 2.69 (s, 3H).

5

**Example 168** (General procedure 1)

Methyl-phenyl-carbamic acid isoquinolin-1-yl ester

The title product was prepared from and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC. (15%, colourless oil). HPLC-MS:  $m/z$  = 279.1 (M+1);  $R_f$ : 3.67 min.

10

**Example 169** (General procedure 1)

Methyl-phenyl-carbamic acid 3-phenoxy-phenyl ester

15

The title product was prepared from 3-phenoxyphenol and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC. (79%, colourless oil).

HPLC-MS:  $m/z$  = 320.1 (M+1);  $R_f$ : 5.16 min.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.20-7.50 (m, 8 H), 7.11 (t, 1H), 6.95-7.06 (m, 2H), 6.70-6.93 (m, 3H), 3.40 (s, 3H).

20

**Example 170** (General procedure 1)

Methyl-phenyl-carbamic acid 3-acetyl-phenyl ester

The title product was prepared from m-hydroxyacetophenone and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (62%, colourless oil). HPLC-MS:  $m/z$  = 270.1 (M+1);  $R_f$ : 3.56 min.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.78 (d, 1H), 7.68 (s, 1H), 7.22-7.50 (m, 7H), 3.43 (s, 3H), 2.58 (s, 3H).

25

**Example 171** (General procedure 1)

Methyl-phenyl-carbamic acid 4-acetyl-2-carbamoyl-phenyl ester

30

The title product was prepared from 5-acetylsalicylamide and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC. (87%, white solid).

HPLC-MS:  $m/z$  = 313.1 (M+1);  $R_f$ : 2.51 min.

35

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.47 (bs, 1H), 8.08 (dd, 1H), 7.30-7.52 (m, 6H), 6.05 (bs, 1H), 5.38 (bs, 1H), 3.43 (s, 3H), 2.61 (s, 3H).

**Example 172** (General procedure 1)

5 Methyl-phenyl-carbamic acid 4-acetyl-3-methyl-phenyl ester

The title product was prepared from 4'-hydroxy-2'-methylacetophenone and N-methyl-N-phenylcarbonyl chloride. The crude product was subjected to preparative HPLC. (76%, white crystals). HPLC-MS: *m/z* = 284.2 (M+1); *R<sub>t</sub>*: 3.95 min.

10 <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.72 (d, 1H), 7.22-7.47 (m, 5H), 6.90-7.12 (m, 2H), 3.43 (s, 3H), 2.55 (s, 3H), 2.52 (s, 3H).

**Example 173** (General procedure 1)

15 Methyl-phenyl-carbamic acid 1-oxo-indan-4-yl ester

The title product was prepared from 4-hydroxyindanone and N-methyl-N-phenylcarbonyl chloride. The crude product was subjected to preparative HPLC. (77%, light yellow oil).

HPLC-MS: *m/z* = 282.1 (M+1); *R<sub>t</sub>*: 3.54 min.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.61 (d, 1H), 7.27-7.50 (m, 7H), 3.45 (s, 3H), 3.00 (ds, 2H), 2.67 (t, 2H).

20

**Example 174** (General procedure 1)

Methyl-phenyl-carbamic acid benzothiazol-2-yl ester

The title product was prepared from 2-benzothiazolol and N-methyl-N-phenylcarbonyl chloride. The crude product was subjected to preparative HPLC. (70%, white crystals). HPLC-MS: *m/z* = 307.1 (M+1); *R<sub>t</sub>*: 4.24 min, purity 85%.

25

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.78 (m, 2H), 7.28-7.50 (m, 7H), 3.40-3.70 (d, 3H).

**Example 175** (General procedure 1)

30 Methyl-phenyl-carbamic acid 5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl ester

The title product was prepared from 6-hydroxy-1-tetralone and N-methyl-N-phenylcarbonyl chloride. The crude product was subjected to preparative HPLC. (49%, colorless oil). HPLC-MS: *m/z* = 296.2 (M+1); *R<sub>t</sub>*: 3.90 min.

35 <sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.04 (d, 2H), 7.27-7.50 (m, 5H), 7.00-7.10 (m, 2H), 3.42 (s, 3H), 2.94 (t,

2H), 2.63 (t, 2H), 2.12 (qu, 2H).

**Example 176** (General procedure 1)

Methyl-phenyl-carbamic acid benzo[d]isoxazol-3-yl ester

5

The title product was prepared from benzo[d]isoxazol-3-ol and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC. (53%, colorless oil). HPLC-MS:  $m/z$  = 291.1 (M+23);  $R_f$ : 4.05 min.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.60-7.75 (m, 1H), 7.49-7.60 (m, 2H), 7.38-7.48 (m, 4H), 7.28-7.36 (m, 2H),  
10 3.46 (s, 3H).

**Example 177** (General procedure 1)

Methyl-phenyl-carbamic acid pyridin-2-yl ester

15 The title product was prepared from 2-hydroxypyridine and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC. (57%, colorless oil). HPLC-MS:  $m/z$  = 229.1 (M+23);  $R_f$ : 2.80 min.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 8.38 (d, 1H), 7.75 (t, 1H), 7.35-7.45 (m, 4H), 7.22-7.34 (m, 1H), 7.14-7.21 (t, 1H), 6.99-7.15 (bs, 1H), 3.44 (s, 3H).

20

**Example 178** (General procedure 1)

Methyl-phenyl-carbamic acid 1-(methyl-phenyl-carbamoyl)-1H-benzimidazol-2-yl ester

The title product was prepared from 2-hydroxybenzimidazole and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC. (14%, white crystals). HPLC-MS:  $m/z$  = 401.2 (M+1);  $R_f$ : 3.88 min, purity: 83%.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.32 (dd, 2H), 7.24-7.28 (m, 2H), 7.21-7.24 (m, 2H), 7.29 (t, 1H), 7.12-7.19 (m, 5H), 7.09-7.15 m, 2H), 3.28 (s, 6H).

30 **Example 179** (General procedure 1)

Methyl-phenyl-carbamic acid 4-[(pyridine-3-carbonyl)-amino]-phenyl ester

The title product was prepared from N-(4-Hydroxy-phenyl)-nicotinamide and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC. (1%, light  
35 yellow crystals). HPLC-MS:  $m/z$  = 348.1 (M+1);  $R_f$ : 2.96 min.



**Example 180** (General procedure 11)

4-Pyrrolidin-1-yl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

5 The title product was prepared from 4-(5-trifluoromethyl-pyridin)-2-yloxy)-phenol and 4-(1-pyrrolidinyl)piperidine. The crude product was used without further purification (68%, white solid). HPLC-MS:  $m/z$  = 436.2 (M+1);  $R_t$ : 2.98 min.

$^1\text{H}$  NMR (DMSO- $d_6$ ): 10.90 (bs, 1H), 8.57 (s, 1H), 8.24 (dd, 1H), 7.15-7.30 (m, 5H), 4.00-4.40 (m, 2H), 3.45-3.60 (m, 2H), 2.75-3.25 (m, 4H), 2.05-2.25 (d, 2H), 1.80-2.05 (m, 5H),

10 1.60-1.80 (m, 2H).

**Example 181** (General procedure 12)

Methyl-o-tolyl-carbamic acid 4-(trifluoromethyl-pyridin-2-yloxy)-phenyl ester

15 The title product was prepared from 4-(5-trifluoromethyl-pyridin)-2-yloxy)-phenol and N-methyl-o-toluidine. The crude product was subjected to preparative HPLC (51%, colorless oil). HPLC-MS:  $m/z$  = 403.2 (M+1);  $R_t$ : 4.89 min.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 8.40 (s, 1H), 7.87 (dd, 1H), 7.05-7.18 (m, 4H), 6.96 (d, 1H), 3.30 (s, 3H), 2.36 (s, 3H).

20

**Example 182** (General procedure 12)

Methyl-pyridin-2-yl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title product was prepared from 4-(5-trifluoromethyl-pyridin)-2-yloxy)-phenol and 2-(methylamino)pyridine. The crude product was subjected to preparative HPLC (55%, white solid). HPLC-MS:  $m/z$  = 390.1 (M+1);  $R_t$ : 4.31 min.

25

**Example 183** (General procedure 12)

Methyl-m-tolyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

30

The title product was prepared from 4-(5-trifluoromethyl-pyridin)-2-yloxy)-phenol and N-methyl-m-toluidine. The crude product was subjected to preparative HPLC (51%, colorless oil). HPLC-MS:  $m/z$  = 403.2 (M+1);  $R_t$ : 4.98 min.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 8.42 (s, 1H), 7.88 (dd, 1H), 7.28 (d, 1H), 7.05-7.25 (m, 7H), 6.97 (d, 1H), 3.41 (s, 3H), 2.38 (s, 3H).

35

**Example 184** (General procedure 12)

(3-Chloro-phenyl)-methyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

5 The title product was prepared from 4-(5-trifluoromethyl-pyridin)-2-yloxy)-phenol and 3-chloro-N-methylaniline. The crude product was subjected to preparative HPLC (54%, colorless oil). HPLC-MS:  $m/z$  = 423.1 (M+1);  $R_t$ : 5.07 min.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 8.42 (m, 1H), 7.88 (dd, 1H), 7.39 (m, 1H), 7.33 (t, 1H), 7.22-7.30 (m, 2H), 7.10-7.7.22 (m, 4H), 6.99 (d, 1H), 3.43 (s, 3H).

10

**Example 185** (General procedure 12)

Methyl-p-tolyl-carbamic acid 4-(5-trifluoromethyl -pyridin-2-yloxy)-phenyl ester

The title product was prepared from 4-(5-trifluoromethyl-pyridin)-2-yloxy)-phenol and N-methyl-p-toluidine. The crude product was subjected to preparative HPLC (54%, white solid).  
15 HPLC-MS:  $m/z$  = 403.2 (M+1);  $R_t$ : 4.99 min.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 8.42 (s, 1H), 7.87 (dd, 1H), 7.05-7.30 (m, 8H), 6.98 (d, 1H), 3.40 (s, 3H), 2.36 (s, 3H).

20 **Example 186** (General procedure 14)

Methyl-phenyl-carbamic acid 4-(3-pyridin-3-yl-acryloyl)-phenyl ester

The title product was prepared from 1-(4-hydroxy-phenyl)-3-pyridin-3-yl-prop-2-en-1-one and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative  
25 HPLC (56%, off-white solid). HPLC-MS:  $m/z$  = 359.0 (M+1);  $R_t$ : 3.27 min.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 8.87 (d, 1H), 8.65 (dd, 1H), 8.03 (d, 2H), 7.97 (dt, 1H), 7.79 (d, 1H), 7.57 (d, 1H), 7.33-7.47 (m, 5H), 7.27-7.33 (m, 3H), 3.44 (s, 3H), 3.49 (t, 1H), 1.21 (t, 1H).

**Example 187** (General procedure 14)30 

Methyl-phenyl-carbamic acid 4-[3-(3,4,5-trimethoxy-phenyl)-acryloyl]-phenyl ester

The title product was prepared from 1-(4-hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (82%, yellow solid). HPLC-MS:  $m/z$  = 448.2 (M+1);  $R_t$ : 4.61 min.

35 

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 8.01 (d, 2H), 7.70 (d, 1H), 7.33-7.47 (m, 4H), 7.28-7.33 (m, 2H), 6.86 (s,

1H), 3.92 (s, 6H), 3.90 (s, 3H), 3.45 (s, 3H).

**Example 188** (General procedure 14)

Methyl-phenyl-carbamic acid 4-diethylcarbamoyl-2-methoxy-phenyl ester

5

The title product was prepared from N,N-diethyl-4-hydroxy-3-methoxy-benzamide and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (58%, colorless oil). HPLC-MS:  $m/z$  = 357.1 (M+1);  $R_t$ : 3.64 min.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.34-7.44 (m, 4H), 7.21-7.28 (m, 1H), 7.03-7.09 (d, 1H), 6.99 (d, 1H), 6.90 (dd, 1H), 3.87 (s, 3H), 3.15-3.65 (bs, 4H), 3.43 (s, 3H), 1.05-1.35 (m, 6H).

10

**Example 189** (General procedure 14)

Methyl-phenyl-carbamic acid 3-phenylcarbamoyl-phenyl ester

15 The title product was prepared from 3-hydroxy-N-phenyl-benzamide and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (54%, white solid). HPLC-MS:  $m/z$  = 347.2 (M+1);  $R_t$ : 4.01 min.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.76 (s, 1H), 7.68 (d, 1H), 7.58-7.65 (m, 3H), 7.27-7.51 (m, 8H), 7.15 (t, 1H), 3.44 (s, 3H).

20

**Example 190** (General procedure 14)

Methyl-phenyl-carbamic acid quinolin-7-yl ester

25 The title product was prepared from 7-hydroxyquinoline and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (28%, white solid). HPLC-MS:  $m/z$  = 279.1 (M+1);  $R_t$ : 2.55 min.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 8.93 (dd, 1H), 8.18 (d, 1H), 7.83-7.86 (m, 1H), 7.82 (d, 1H), 7.35-7.50 (m, 6H), 7.27-7.32 (m, 1H), 3.47 (s, 1H).

30 **Example 191** (General procedure 14)

Methyl-phenyl-carbamic acid 4-(4-methyl-piperazine-1-carbonyl)-phenyl ester

The title product was prepared from 1-(4-hydroxybenzoyl)-4-methyl-piperazine and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (22%, colorless oil). HPLC-MS:  $m/z$  = 354.1 (M+1);  $R_t$ : 2.07 min.

35

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.37-7.49 (m, 4H), 7.28-7.37 (m, 3H), 7.16-7.25 (m, 2H), 4.60-4.00 (bs, 2H), 3.43 (s, 3H), 3.35-3.90 (bs, 4H), 2.82 (s, 3H) 2.55-2.90 (bs, 2H).

**Example 192** (General procedure 14)

5 **Methyl-phenyl-carbamic acid 3-acetylamino-phenyl ester**

The title product was prepared from 3-acetamidophenol and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (66%, white solid). HPLC-MS:  $m/z$  = 285.1 (M+1);  $R_t$ : 3.09 min.

10  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.40-7.49 (m, 1H), 7.31-7.40 (m, 5H), 7.25-7.30 (m, 1H), 7.22 (d, 1H), 7.14 (d, 1H), 6-84 (bd, 1H), 3.42 (s, 3H), 2.10 (s, 3H).

**Example 193** (General procedure 14)

15 **Methyl-phenyl-carbamic acid 4-benzoyl-phenyl ester**

The title product was prepared from (4-hydroxy-phenyl)-phenyl-methanone and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (36%, colorless oil). HPLC-MS:  $m/z$  = 332.2 (M+1);  $R_t$ : 4.42 min.

20  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.75-7.85 (m, 4H), 7.58 (tt, 1H), 7.33-7.52 (m, 6H), 7.27-7.32 (m, 1H), 7.18-7.25 (m, 2H), 3.44 (s, 3H).

**Example 194** (General procedure 14)

**Methyl-phenyl-carbamic acid biphenyl-3-yl ester**

25 The title product was prepared from 3-phenylphenol and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (52%, colorless oil). HPLC-MS:  $m/z$  = 304.2 (M+1);  $R_t$ : 4.75 min.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.52-7.67 (m, 2H), 7.22-7.52 (m, 11H), 7.03-7.22 (m, 1H), 3.45 (s, 3H).

30 **Example 195** (General procedure 14)

**Methyl-phenyl-carbamic acid 1H-indol-4-yl ester**

The title product was prepared from 4-hydroxyindole and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (48%, off-white solid). HPLC-

35 MS:  $m/z$  = 267.1 (M+1);  $R_t$ : 3.57 min.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.20 (ds, 1H), 7.36-7.50 (m, 4H), 7.17-7.35 (m, 2H), 7.08-7.17 (m, 2H), 6.94 (d, 1H), 6.44 (s, 1H), 3.48 (s, 3H).

**Example 196** (General procedure 14)

5 Methyl-phenyl-carbamic acid 5,6,7,8-tetrahydro-naphthalen-1-yl ester

The title product was prepared from 5,6,7,8-tetrahydro-1-naphthol and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (42%, colorless oil). HPLC-MS: *m/z* = 282.1 (M+1); R<sub>t</sub>: 4.77 min.

10 <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.33-7.45 (m, 4H), 7.22-7.32 (m, 1H), 7.02-7.13 (t, 1H), 6.82-7.96 (m, 2H), 3.42 (s, 3H), 2.70-2.82 (m, 2H), 2.50-2.65 (m, 2H), 1.62-1.83 (m, 4H).

**Example 197** (General procedure 14)

Methyl-phenyl-carbamic acid 5-oxo-5,6,7,8-tetrahydro-naphthalen-1-yl ester

15

The title product was prepared from 5,6,7,8-tetrahydro-1-naphthol and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (60%, colorless oil). HPLC-MS: *m/z* = 296.1 (M+1); R<sub>t</sub>: 3.81 min.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.91 (dd, 1H), 7.21-7.50 (m, 7H), 3.44 (s, 3H), 2.60-2.93 (bs, 2H), 2.62 (t, 20 2H), 2.02-2.20 (m, 2H).

**Example 198** (General procedure 14)

Methyl-phenyl-carbamic acid 1,3-dioxo-1,3-dihydro-isobenzofuran-4-yl ester

25 The title product was prepared from 4-hydroxy-isobenzofuran-1,3-dione and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (50%, white solid). HPLC-MS: *m/z* = 298.1 (M+1); R<sub>t</sub>: 2.58 min, purity: 85%.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.90 (d, 1H), 7.48-7.62 (m, 2H), 7.28-7.45 (m, 5H), 3.38 (s, 3H).

30 **Example 199** (General procedure 1)

Methyl-phenyl-carbamic acid 4-(5-chloro-pyridin-2-yloxy)-phenyl ester

The title product was prepared from 4-(5-chloro-pyridin-2-yloxy)-phenol and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to column chromatography  
35 (ethyl acetate/heptane (1:5) (85%, white solid). HPLC-MS: *m/z* = 355.1 (M+1); R<sub>t</sub>: 4.56 min.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.10 (d, 1H), 7.62 (dd, 1H), 7.31-7.44 (m, 4H), 7.25-7.30 (m, 1H), 7.05-7.20 (m, 4H), 6.84 (d, 1H), 3.43 (s, 3H).

**Example 200** (General procedure 14)

5 (3-Fluoro-phenyl)-methyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title product was prepared from 4-(5-Trifluoromethyl-pyridin-2-yloxy)-phenol and 3-fluoro-N-methylaniline. The crude product was subjected to preparative HPLC (31%, white solid).

HPLC-MS: *m/z* = 407.0 (M+1); *R<sub>t</sub>*: 4.93 min.

10 <sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.42 (s, 1H), 7.88 (dd, 1H), 7.36 (q, 1H), 7.07-7.24 (m, 6H), 7.00 (d, 1H), 7.92-7.05 (m, 1H), 3.44 (s, 3H).

**Example 201** (General procedure 11)

15 4-Benzyl-piperazine-1-carboxylic acid 4-(5-chloro-pyridin-2-yloxy)-phenyl ester

The title product was prepared from 4-(5-chloro-pyridin-2-yloxy)-phenol and 1-benzylpiperazine. The title product precipitated from the reaction mixture and was collected by filtration (88%, off-white solid). HPLC-MS: *m/z* = 424.1 (M+1); *R<sub>t</sub>*: 2.91 min.

20 <sup>1</sup>H NMR (CDCl<sub>3</sub>): 13.86 (bs, 1H), 8.11 (d, 1H), 7.60-7.70 (m, 3H), 7.45-7.55 (m, 3H), 7.05-7.20 (m, 4H), 6.98 (d, 1H), 4.26-4.40 (m, 2H), 4.15-4.25 (m, 2H), 3.38-3.53 (m, 2H), 3.60-4.15 (m, 2H), 2.72-2.92 (m, 2H).

**Example 202** (General procedure 11)

25 4-Pyridin-3-ylmethyl-piperazine-1-carboxylic acid 4-(5-chloro-pyridin-2-yloxy)-phenyl ester

The title product was prepared from 4-(5-chloro-pyridin-2-yloxy)-phenol and (3-pyridylmethyl)piperazine. The title product precipitated from the reaction mixture and was collected by filtration and recrystallized from ethanol (35%, off-white solid). HPLC-MS: *m/z* = 425.2 (M+1); *R<sub>t</sub>*: 2.39 min.

30 <sup>1</sup>H NMR (CDCl<sub>3</sub>): 13.00-14.50 (bs, 1H), 8.72 (d, 2H), 8.50 (bs, 1H), 8.11 (d, 1H), 7.64 (dd, 1H), 7.56 (bs, 1H), 7.06-7.14 (m, 4H), 6.88 (d, 1H), 3.6-4.4 (m, 6H), 2.70-3.50 (m, 4H).

**Example 203** (General procedure 14)

35 4-Hydroxymethyl-piperidine-1-carboxylic acid 4-(5-chloro-pyridin-2-yloxy)-phenyl ester

The title product was prepared from 4-(5-chloro-pyridin-2-yloxy)-phenol and 4-hydroxymethyl-piperidine. The crude product was subjected to column chromatography (ethyl acetate/heptane, 1:1) (75%, colorless oil). HPLC-MS:  $m/z$  = 363.1 (M+1);  $R_t$ : 3.58 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 8.12 (d, 1H), 7.64 (dd, 1H), 7.05-7.24 (m, 4H), 6.85 (d, 1H), 4.33 (ds, 2H), 3.56 (t, 2H), 2.75-3.10 (m, 2H), 1.69-1.95 (m, 3H), 1.56 (s, 1H), 1.19-1.45 (m, 2H).

**Example 204** (General procedure 1)

Methyl-phenyl-carbamic acid 4-morpholin-4-yl-phenyl ester

The title product was prepared from and 4-morpholin-4-yl-phenol and N-methyl-N-phenylcarbonyl chloride. The crude product was extracted with dichloromethane from citric acid (5%). The combined organic phases were evaporated and the product crystallized from ethanol (22%, crystals). HPLC-MS:  $m/z$  = 313.2 (M+1);  $R_t$ : 3.75 min.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ): 7.35-7.50 (m, 4H), 7.22-7.32 (m, 1H), 7.00 (d, 2H), 6.92 (d, 2H), 3.72 (t, 4H), 3.32 (s, 3H), 3.05 (t, 4H).

**Example 205** (General procedure 1)

1,4-Dioxo-8-aza-spiro[4.5]decane-8-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

20

The title product was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 4-piperidone ethylene ketal. The crude product was extracted with dichloromethane from citric acid (5%). The combined organic phases were evaporated and the product crystallized from ethanol (61%, crystals). HPLC-MS:  $m/z$  = 425.2 (M+1);  $R_t$ : 4.45 min.

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**Example 206** (General procedure 14)

The title product was prepared from 2-(4-hydroxy-phenyl)-indan-1,3-dione and N-methyl-N-phenylcarbonyl chloride. The crude product was subjected to preparative HPLC (1%, oil). HPLC-MS:  $m/z$  = 372.1 (M+1);  $R_t$ : 4.80 min.

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**Example 207** (General procedure 14)

Methyl-phenyl-carbamic acid 4-(5,6-dichloro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-phenyl ester

The title product was prepared from 5,6-dichloro-2-(4-hydroxy-phenyl)-isoindole-1,3-dione

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and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (2%,). HPLC-MS:  $m/z$  = 441.1 (M+1);  $R_t$ : 5.00 min.

**Example 208** (General procedure 14)

5 Methyl-phenyl-carbamic acid 4-(2-phenoxy-acetyl-amino)-phenyl ester

The title product was prepared from N-(4-hydroxy-phenyl)-2-phenoxy-acetamide and N-methyl-N-phenylcarbamoyl chloride. The crude product was purified by preparative HPLC (54%, oil). HPLC-MS:  $m/z$  = 277.2 (M+1);  $R_t$ : 4.19 min.

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**Example 209** (General procedure 14)

Methyl-phenyl-carbamic acid 4-[2-(4-chloro-phenyl)-ethyl]-phenyl ester

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The title product was prepared from 4-(4-chlorophenethyl)-phenol and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (57%, white crystals). HPLC-MS:  $m/z$  = 366.1 (M+1);  $R_t$ : 5.58 min.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.31-7.45 (m, 4H), 7.17-7.30 (m, 3H), 6.96-7.12 (m, 6H), 3.41 (s, 3H), 2.85 (s, 4H).

20 **Example 210** (General procedure 14)

Methyl-phenyl-carbamic acid 4-[(pyridine-2-carbonyl)-amino]-phenyl ester

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The title product was prepared from pyridine-2-carboxylic acid (4-hydroxy-phenyl)-amide and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (41%,). HPLC-MS:  $m/z$  = 348.1 (M+1);  $R_t$ : 4.00 min.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.32-7.47 (m, 4H), 7.24-7.31 (m, 3H), 7.10-7.23 (m, 4H), 7.79 (d, 2H), 3.41 (m, 6H).

**Example 211** (General procedure 14)

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Methyl-phenyl-carbamic acid 4-[methyl-(thiophene-2-carbonyl)-amino]-phenyl ester

The title product was prepared from thiophene-2-carboxylic acid (4-hydroxy-phenyl)-methyl-amide and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (16%, oil). HPLC-MS:  $m/z$  = 367.2 (M+1);  $R_t$ : 3.97 min.

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**Example 212** (General procedure 14)

Methyl-phenyl-carbamic acid 4-butyrylamino-phenyl ester

The title product was prepared from 4'-hydroxybutyranilide and N-methyl-N-phenylcarbamo-  
5 chloride. The crude product was subjected to preparative HPLC (60%, white solid). HPLC-  
MS:  $m/z$  = 313.2 (M+1);  $R_t$ : 3.58 min.

**Example 213** (General procedure 14)

Methyl-phenyl-carbamic acid 4-(4,6-dimethyl-pyrimidin-2-ylsulfanyl)-phenyl ester

10 The title product was prepared from 4-(4,6-dimethylpyrimidin-2-ylsulfanyl)-phenol and N-  
methyl-N-phenylcarbamo-yl chloride. The crude product was subjected to preparative HPLC  
(59%, white solid). HPLC-MS:  $m/z$  = 366.1 (M+1);  $R_t$ : 4.50 min.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.59 (d, 2H), 7.32-7.45 (m, 4H), 7.23-7.31 (m, 1H), 7.16 (d, 2H), 6.68 (s,  
15 1H), 3.43 (s, 1H), 2.32.

**Example 214** (General procedure 14)

Methyl-phenyl-carbamic acid 4-methanesulfonyl-phenyl ester

20 The title product was prepared from 4-methylsulfonylphenol and N-methyl-N-  
phenylcarbamo-yl chloride. The crude product was subjected to preparative HPLC (50%,  
white solid). HPLC-MS:  $m/z$  = 306.1 (M+1);  $R_t$ : 3.22 min.

**Example 215** (General procedure 14)

25 Methyl-phenyl-carbamic acid 4-[2-(3-oxo-1,2,3,4-tetrahydro-quinoxalin-2-yl)-acetylamino]-  
phenyl ester

The title product was prepared from N-(4-hydroxyphenyl)-2-(3-oxo-1,2,3,4-tetrahydro-2-  
quinoxaliny)acetamide and N-methyl-N-phenylcarbamo-yl chloride. The crude product was  
30 subjected to preparative HPLC (20%, yellow solid). HPLC-MS:  $m/z$  = 431.2 (M+1);  $R_t$ : 3.55  
min.

**Example 216** (General procedure 14)

Methyl-phenyl-carbamic acid 4-phenylacetyl-phenyl ester

The title product was prepared from benzyl 4-hydroxyphenyl ketone and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (68%, light yellow oil). HPLC-MS:  $m/z$  = 431.2 (M+1);  $R_t$ : 3.55 min.

5 **Example 217** (General procedure 12)

4-Benzoyl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title product was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 4-benzoylpiperidine (29%, white solid). HPLC-MS:  $m/z$  = 471.3 (M+1);  $R_t$ : 5.12 min.

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**Example 218** (General procedure 11)

[1,4']Bipiperidinyl-1'-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

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The title product was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenol and 4-piperidinopiperidine. The crude product was filtered from the reaction mixture and washed with diethyl ether to give the title product (50%, off-white solid). HPLC-MS:  $m/z$  = 450.1 (M+1);  $R_t$ : 3.12 min.

**Example 219** (General procedure 12)

20 4-(2-Oxo-2,3-dihydro-benzimidazol-1-yl)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title product was prepared from 4-(5-Trifluoromethyl-pyridin-2-yloxy)-phenol and 1-piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (44%, oil). HPLC-MS:  $m/z$  = 499.1 (M+1);  $R_t$ : 4.35 min.

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$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 10.15 (s, 1H), 8.44 (s, 1H), 7.90 (dd, 1H), 7.23 (t, 1H), 7.13-7.20 (m, 4H), 7.06-7.13 (m, 2H), 7.02 (d, 1H), 4.40-4.70 (m, 3H), 2.95-3.30 (m, 2H), 2.40-2.63 (m, 2H), 1.86 (d, 2H).

30 **Example 220** (General procedure 12)

3-Diethylcarbamoyl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title product was prepared from 4-(5-Trifluoromethyl-pyridin-2-yloxy)-phenol and N,N-diethylnipecotamide (56%, oil). HPLC-MS:  $m/z$  = 466.1 (M+1);  $R_t$ : 4.51 min.

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**Example 221** (General procedure 12)

4-Carbamoyl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

- 5 The title product was prepared from 4-(5-Trifluoromethyl-pyridin-2-yloxy)-phenol and piperidine-4-carboxylic acid amide. The crude product was subjected to preparative HPLC (47%, white solid). HPLC-MS:  $m/z$  = 410.2 (M+1);  $R_t$ : 3.45 min.

**Example 222** (General procedure 12)

- 10 3-Carbamoyl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title product was prepared from 4-(5-Trifluoromethyl-pyridin-2-yloxy)-phenol and nipecotamide. The crude product was purified by preparative HPLC (60%, white solid). HPLC-MS:  $m/z$  = 410.2 (M+1);  $R_t$ : 3.45 min.

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**Example 223** (General procedure 14)

Methyl-phenyl-carbamic acid 4-[[4-(methyl-phenyl-carbamoyloxy)-2-oxo-1,2-dihydro-quinoline-3-carbonyl]-amino]-phenyl ester

- 20 The title product was prepared from 4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid (4-hydroxyphenyl)-amide and N-methyl-N-phenylcarbamoyl chloride. The crude product was subjected to preparative HPLC (6.6 %, oil). HPLC-MS:  $m/z$  = 563.2 (M+1);  $R_t$ : 4.46 min.  
 $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 8.38 (d, 1H), 7.75 (t, 1H), 7.35-7.45 (m, 4H), 7.22-7.34 (m, 1H), 7.14-7.21 (t, 1H), 6.99-7.15 (bs, 1H), 3.44 (s, 3H).

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**Example 224** (General procedure 14)

Methyl-phenyl-carbamic acid 4-[(4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carbonyl)-amino]-phenyl ester

- 30 The title product was prepared from 4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid (4-hydroxy-phenyl)-amide and N-methyl-N-phenylcarbamoyl chloride (5%,). HPLC-MS:  $m/z$  = 430.1 (M+1);  $R_t$ : 4.80 min, purity: 70%.

**Example 225** (General procedure 14)

- 35 Methyl-phenyl-carbamic acid 4-(4-hydroxy-benzyl)-phenyl ester

The title compound was prepared from 4,4'-dihydroxydiphenylmethane and N-methyl-N-phenylcarbonyl chloride. The crude product was subjected to preparative HPLC (21 %, white crystals which turn red after standing). HPLC-MS:  $m/z$  = 324.2 (M+1);  $R_t$ : 4.21 min.

5 **Example 226** (General procedure 13)

Methyl-phenyl-carbamic acid 4-(4-trifluoromethyl-benzylcarbonyl)-phenyl ester

The title product was prepared from 4-(methyl-phenyl-carbamoyloxy)-benzoic acid 2,5-dioxo-pyrrolidin-1-yl ester and 4-trifluoromethyl-benzylamine (94%, white crystals). HPLC-MS:  $m/z$  = 429.2 (M+1);  $R_t$ : 4.35 min.

**Example 227** (General procedure 13)

Methyl-phenyl-carbamic acid 4-(butyl-methyl-carbamoyl)-phenyl ester

15 The title product was prepared from 4-(methyl-phenyl-carbamoyloxy)-benzoic acid 2,5-dioxo-pyrrolidin-1-yl ester and *n*-butyl-methyl-amine. The crude product was subjected to preparative HPLC (20%, oil). HPLC-MS:  $m/z$  = 341.2 (M+1);  $R_t$ : 3.96 min.

**Example 228** (General procedure 13)

20 Methyl-phenyl-carbamic acid 4-(methyl-phenethyl-carbamoyl)-phenyl ester

The title product was prepared from 4-(methyl-phenyl-carbamoyloxy)-benzoic acid 2,5-dioxo-pyrrolidin-1-yl ester and methyl-phenethyl-amine. The crude product was subjected to preparative HPLC (29 %, oil). HPLC-MS:  $m/z$  = 389.2 (M+1);  $R_t$ : 4.15 min.

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**Example 229** (General procedure 13)

Methyl-phenyl-carbamic acid 4-[(pyridin-2-ylmethyl)-carbonyl]-phenyl ester

The title product was prepared from 4-(methyl-phenyl-carbamoyloxy)-benzoic acid 2,5-dioxo-pyrrolidin-1-yl ester and 2-aminomethylpyridine. The crude product was used without further purification (57%, oil). HPLC-MS:  $m/z$  = 362.2 (M+1);  $R_t$ : 2.43 min.

$^1\text{H}$  NMR (MeOH- $d_4$ ): 8.50 (d, 1H), 7.92 (d, 2H), 7.83 (dt, 1H), 7.38-7.50 (m, 5H), 7.26-7.37 (m, 2H), 7.15-7.26 (m, 2H), 4.69 (s, 2H), 3.41 (s, 3H).

35 **Example 230** (General procedure 13)

**Methyl-phenyl-carbamic acid 4-(2-pyridin-2-yl-ethylcarbamoyl)-phenyl ester**

- The title product was prepared from 4-(methyl-phenyl-carbamoyloxy)-benzoic acid 2,5-dioxo-pyrrolidin-1-yl ester and 2-aminoethylpyridine. The crude product was used without further purification (26%, oil). HPLC-MS:  $m/z$  = 376.2 (M+1);  $R_t$ : 2.25 min.
- $^1\text{H}$  NMR (MeOH- $d_4$ ): 8.51 (d, 1H), 7.87 (dt, 1H), 7.78 (d, 2H), 7.33-7.50 m, 6H), 7.25-7.33 (m, 1H), 7.18 (d, 2H), 3.74 (t, 2H), 3.41 (bs, 3H), 3.13 (t, 2H).

**Example 231 (General procedure 13)**

- 10 **Methyl-phenyl-carbamic acid 4-(2-phenylamino-ethylcarbamoyl)-phenyl ester**

- The title product was prepared from 4-(methyl-phenyl-carbamoyloxy)-benzoic acid 2,5-dioxo-pyrrolidin-1-yl ester and N-phenylethylenediamine. The crude product was used without further purification (80%, off-white foam). HPLC-MS:  $m/z$  = 390.2 (M+1);  $R_t$ : 3.51 min.
- 15  $^1\text{H}$  NMR (MeOH- $d_4$ ): 7.82 (d, 2H), 7.36-7.48 (m, 4H), 7.22-7.34 (m, 1H), 7.15-7.22 (d, 2H), 7.10 (t, 2H), 6.69 (d, 2H), 6.62 (t, 1H), 3.72 (t, 2H), 3.57 (t, 2H), 3.40 (s, 3H), 3.20 (s, 1H).

**Example 232 (General procedure 13)****Methyl-phenyl-carbamic acid 4-(3-methyl-butylcarbamoyl)-phenyl ester**

- 20 The title product was prepared from 4-(methyl-phenyl-carbamoyloxy)-benzoic acid 2,5-dioxo-pyrrolidin-1-yl ester and *iso*-amylamine. The crude product was used without further purification (95%, oil). HPLC-MS:  $m/z$  = 341.2 (M+1);  $R_t$ : 3.99 min.
- $^1\text{H}$  NMR (MeOH- $d_4$ ): 7.82 (d, 2H), 7.36-7.50 (m, 4H), 7.26-7.35 (m, 1H), 7.15-7.24 (d, 2H), 3.34-3.46 (m, 5H), 1.67 (sept, 1H), 1.50 (q, 2H), 0.96 (d, 6H).
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**Example 233 (General procedure 13)****Methyl-phenyl-carbamic acid 4-(3,3-dimethyl-butylcarbamoyl)-phenyl ester**

- 30 The title product was prepared from 4-(methyl-phenyl-carbamoyloxy)-benzoic acid 2,5-dioxo-pyrrolidin-1-yl ester and 3,3-dimethylbutylamine. The crude product was used without further purification (88%, oil). HPLC-MS:  $m/z$  = 355.1 (M+1);  $R_t$ : 3.10 min.
- $^1\text{H}$  NMR (MeOH- $d_4$ ): 7.82 (d, 2H), 7.36-7.50 (m, 4H), 7.25-7.35 (m, 1H), 7.15-7.25 (d, 2H), 3.33-3.47 (m, 5H), 1.49-1.57 (m, 2H), 0.97 (s, 9H).

**Example 234** (General procedure 13)

Methyl-phenyl-carbamic acid 4-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-phenyl ester

The title product was prepared from 4-(methyl-phenyl-carbamoyloxy)-benzoic acid 2,5-dioxo-  
pyrrolidin-1-yl ester and C-(tetrahydro-furan-2-yl)methylamine. The crude product was used  
without further purification (86%, oil). HPLC-MS:  $m/z = (M+1)$ ;  $R_t$ : min.

$^1\text{H}$  NMR (MeOH- $d_4$ ): 7.84 (d, 2H), 7.35-7.50 (m, 4H), 7.25-7.35 (m, 1H), 7.12-7.25 (d, 2H),  
4.10 (qui, 1H), 3.87 (q, 1H), 3.68-3.82 (m, 1H), 3.41 (s, 3H), 3.35-3.54 (m, 2H), 1.82-2.10 (m,  
3H), 1.58-1.72 (m, 1H).

**Example 235** (General procedure 13)

Methyl-phenyl-carbamic acid 4-cyclohexylcarbamoyl-phenyl ester

The title product was prepared from 4-(methyl-phenyl-carbamoyloxy)-benzoic acid 2,5-dioxo-  
pyrrolidin-1-yl ester and cyclohexylamine. The crude product was used without further purifi-  
cation (79%, off-white crystals). HPLC-MS:  $m/z = 353.2 (M+1)$ ;  $R_t$ : 3.98 min.

$^1\text{H}$  NMR (MeOH- $d_4$ ): 8.18 (d, 1H), 7.85 (d, 2H), 7.36-7.52 (m, 4H), 7.25-7.33 (m, 1H), 7.20 (d,  
2H), 3.74 (m, 1H), 1.77-1.88 (m, 2H), 1.65-1.77 (m, 2H), 1.60 (d, 1H), 1.24-1.40 (m, 4H), 1-  
07-1.23 (m, 1H).

**Example 236** (General procedure 13)

Methyl-phenyl-carbamic acid 4-cyclopropylcarbamoyl-phenyl ester

The title product was prepared from 4-(methyl-phenyl-carbamoyloxy)-benzoic acid 2,5-dioxo-  
pyrrolidin-1-yl ester and cyclopropylamine. The crude product was used without further purifi-  
cation (97%, oil). HPLC-MS:  $m/z = 311.2 (M+1)$ ;  $R_t$ : 3.21 min.

$^1\text{H}$  NMR (MeOH- $d_4$ ): 7.81 (d, 2H), 7.36-7.50 (m, 4H), 7.25-7.36 (m, 1H), 7.18 (d, 2H), 3.40  
(bs, 3H), 2.78-2.87 (m, 1H), 0.75-0.85 (m, 2H), 0.57-0.65 (m, 2H).

**Example 237** (General procedure 13)

Methyl-phenyl-carbamic acid 4-(cyclohexylmethyl-carbamoyl)-phenyl ester

The title product was prepared from 4-(methyl-phenyl-carbamoyloxy)-benzoic acid 2,5-dioxo-  
pyrrolidin-1-yl ester and C-cyclohexyl-methylamine. The crude product was used without fur-  
ther purification (84%, oil). HPLC-MS:  $m/z = 367.3 (M+1)$ ;  $R_t$ : 4.28 min.

<sup>1</sup>H NMR (MeOH-d<sub>4</sub>): 7.81 (d, 2H), 7.36-7.49 (m, 4H), 7.25-7.32 (m, 1H), 7.19 (d, 2H), 3.40 (bs, 3H), 3.20 (d, 2H), 1.55-1.82 (m, 5H), 1.13-1.35 (m, 4H), 0.90-1.10 (m, 2H).

#### Example 238

##### 5 Methyl-phenyl-carbamic acid 5-nitro-pyridin-2-yl ester

A solution of 2-hydroxy-5-nitropyridine (1.40 g, 10.0 mmol), 1-methyl-3-(methyl-phenyl-carbamoyl)-3*H*-imidazol-1-ium iodide (3.43 g, 10.0 mmol) and triethylamine (0.42 ml, 10.0 mmol) in acetonitrile (25 ml) was heated at 50 °C for 5 h. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:-heptane (25:75)) followed by crystallisation from ethyl acetate:heptane yielding the title compound (1.13 g, 41% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 3.44 (br.s, 3H), 7.17 (br.d, 1H), 7.27-7.45 (m, 5H), 8.49 (br.d, 1H), 9.19 (br.s, 1H); HPLC-MS (Method A): *m/z* = 296 (M+Na); R<sub>t</sub> = 3.45 min.

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#### Example 239

##### Methyl-phenyl-carbamic acid pyrimidin-2-yl ester

A solution of 2-hydroxypyrimidine hydrochloride (0.40 g, 3.00 mmol), 1-methyl-3-(methyl-phenyl-carbamoyl)-3*H*-imidazol-1-ium iodide (1.03 g, 3.00 mmol) and triethylamine (0.83 ml, 6.00 mmol) in acetonitrile (15 ml) was stirred at room temperature overnight. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate) followed by crystallisation from ethyl acetate:heptane yielding the title compound (0.08 g, 12% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 3.43 (br.s, 3H), 7.14-7.31 (m, 2H), 7.39 (m, 4H), 8.68 (d, 2H); HPLC-MS (Method A): *m/z* = 252 (M+Na); R<sub>t</sub> = 2.32 min.

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#### Example 240

##### Methyl-phenyl-carbamic acid 7-chloro-quinolin-4-yl ester

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A solution of 7-chloro-4-hydroxyquinoline (0.54 g, 3.00 mmol), 1-methyl-3-(methyl-phenyl-carbamoyl)-3*H*-imidazol-1-ium iodide (1.03 g, 3.00 mmol) and triethylamine (0.42 ml, 3.00 mmol) in acetonitrile (15 ml) was stirred at room temperature for 18 hours. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane (40:60)) yielding the title compound (0.87 g, 93% yield) as a colourless

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oil which solidified upon standing.

$^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ ):  $\delta$  3.47 (br.s, 3H), 7.28-7.58 (m, 8H), 8.05 (br.s, 1H), 8.85 (d, 1H); HPLC-MS (Method A):  $m/z$  = 313 (M+H);  $R_t$  = 3.79 min.

#### 5 Example 241

Methyl-phenyl-carbamic acid quinolin-4-yl ester

A mixture of 4-hydroxyquinoline (0.44 g, 3.00 mmol), 1-methyl-3-(methyl-phenyl-carbamoyl)-3H-imidazol-1-ium iodide (1.03 g, 3.00 mmol) and triethylamine (0.42 ml, 3.00 mmol) in acetonitrile (15 ml) was stirred at room temperature for 18 hours. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography ( $\text{SiO}_2$ , ethyl acetate:heptane (50:50)) yielding the title compound (0.75 g, 90% yield) as a white solid.

$^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ ):  $\delta$  3.49 (br.s, 3H), 7.37 (br.t, 1H), 7.41-7.62 (m, 7H), 7.69 (br.t, 1H), 8.08 (br.d, 1H), 8.87 (d, 1H); HPLC-MS (Method A):  $m/z$  = 279 (M+H);  $R_t$  = 2.56 min.

#### Example 242

Methyl-phenyl-carbamic acid 5-methyl-isoxazol-3-yl ester

A mixture of 3-hydroxy-5-methylisoxazole (0.30 g, 3.00 mmol), 1-methyl-3-(methyl-phenyl-carbamoyl)-3H-imidazol-1-ium iodide (1.03 g, 3.00 mmol) and triethylamine (0.42 ml, 3.00 mmol) in acetonitrile (15 ml) was stirred at room temperature for 18 hours. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography ( $\text{SiO}_2$ , ethyl acetate:heptane (25:75)) yielding the title compound (0.67 g, 96% yield) as a colourless oil.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.40 (s, 3H), 3.40 (br.s, 3H), 6.14 (br.s, 1H), 7.28-7.44 (m, 5H); HPLC-MS (Method A):  $m/z$  = 255 (M+Na);  $R_t$  = 3.31 min.

#### Example 243

30 Methyl-phenyl-carbamic acid quinoxalin-2-yl ester

A mixture of 2-hydroxyquinoxaline (0.44 g, 3.00 mmol), 1-methyl-3-(methyl-phenyl-carbamoyl)-3H-imidazol-1-ium iodide (1.03 g, 3.00 mmol) and triethylamine (0.42 ml, 3.00 mmol) in acetonitrile (15 ml) was stirred at room temperature for 18 hours followed by heating at 40 °C for 24 hours. The solvent was evaporated *in vacuo* and the residue was purified



by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane (30:70)) yielding the title compound (0.65 g, 77% yield) as a white solid.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 3.48 (br.s, 3H), 7.29 (m, 1H), 7.41 (m, 4H), 7.72 (m, 2H), 8.00 (m, 1H), 8.10 (m, 1H), 8.67 (br.s, 1H); HPLC-MS (Method A): *m/z* = 280 (M+H); R<sub>t</sub> = 3.66

5 min.

#### Example 244

Methyl-phenyl-carbamic acid 4-methyl-quinolin-2-yl ester

- 10 A mixture of 2-hydroxy-4-methylquinoline (0.48 g, 3.00 mmol), 1-methyl-3-(methyl-phenyl-carbamoyl)-3*H*-imidazol-1-ium iodide (1.03 g, 3.00 mmol) and triethylamine (0.42 ml, 3.00 mmol) in acetonitrile (15 ml) was stirred at room temperature for 18 hours followed by heating at 50 °C for 4 days. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane (30:70)) yielding the title compound (0.24 g, 27% yield) as a white solid.

15 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 2.70 (s, 3H), 3.49 (br.s, 3H), 7.08 (m, 1H), 7.27 (m, 1H), 7.40 (m, 4H), 7.53 (t, 1H), 7.69 (t, 1H), 7.96 (d, 1H), 8.00 (d, 1H); HPLC-MS (Method A): *m/z* = 293 (M+H); R<sub>t</sub> = 3.88 min.

#### 20 Example 245

Methyl-phenyl-carbamic acid 3-methyl-quinoxalin-2-yl ester

- A mixture of 2-hydroxy-3-methylquinoxaline (0.48 g, 3.00 mmol), 1-methyl-3-(methyl-phenyl-carbamoyl)-3*H*-imidazol-1-ium iodide (1.03 g, 3.00 mmol) and triethylamine (0.42 ml, 3.00 mmol) in acetonitrile (15 ml) was stirred at room temperature for 18 hours followed by heating at 50 °C for 3 days. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane (50:50)) yielding the title compound (0.59 g, 67% yield) as a white solid.

- 25 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 2.61 (br.s, 3H), 3.48 (br.s, 3H), 7.30 (m, 1H), 7.42 (m, 4H), 7.69 (m, 2H), 7.99 (m, 2H); HPLC-MS (Method A): *m/z* = 294 (M+H); R<sub>t</sub> = 3.92 min.

#### Example 246

Methyl-phenyl-carbamic acid 4,6-dimethyl-pyrimidin-2-yl ester

- 35 A solution of 4,6-dimethyl-2-hydroxypyrimidine (0.37 g, 3.00 mmol), 1-methyl-3-(methyl-

phenyl-carbamoyl)-3*H*-imidazol-1-ium iodide (1.03 g, 3.00 mmol) and triethylamine (0.42 ml, 3.00 mmol) in acetonitrile (15 ml) was stirred at room temperature for 18 hours. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane (50:50)) yielding the title compound (0.46 g, 60% yield) as a white solid.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 2.48 (s, 6H), 3.43 (br.s, 3H), 6.92 (br.s, 1H), 7.22 (m, 1H), 7.37 (m, 4H); HPLC-MS (Method A): *m/z* = 258 (M+H); *R*<sub>t</sub> = 2.77 min.

#### Example 247

##### 10 Methyl-phenyl-carbamic acid isoquinolin-6-yl ester

A solution of 6-hydroxyquinoline (0.44 g, 3.00 mmol), 1-methyl-3-(methyl-phenyl-carbamoyl)-3*H*-imidazol-1-ium iodide (1.03 g, 3.00 mmol) and triethylamine (0.42 ml, 3.00 mmol) in acetonitrile (15 ml) was stirred at room temperature for 18 hours. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane (50:50)) yielding the title compound (0.80 g, 96% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 3.47 (s, 3H), 7.28 (m, 1H), 7.33-7.54 (m, 6H), 7.59 (s, 1H), 8.08 (d, 2H), 8.86 (m, 1H); HPLC-MS (Method A): *m/z* = 279 (M+H); *R*<sub>t</sub> = 2.63 min.

#### 20 Example 248

##### Methyl-phenyl-carbamic acid quinolin-2-yl ester

A solution of 2-hydroxyquinoline (0.44 g, 3.00 mmol), 1-methyl-3-(methyl-phenyl-carbamoyl)-3*H*-imidazol-1-ium iodide (1.03 g, 3.00 mmol) and triethylamine (0.42 ml, 3.00 mmol) in acetonitrile (15 ml) was stirred at room temperature for 18 hours. More acetonitrile (60 ml) was added and the solution was heated at 50 °C for 3 days. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane (40:60)) yielding the title compound (0.33 g, 40% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 3.50 (br.s, 3H), 7.14-7.30 (m, 2H), 7.42 (m, 4H), 7.52 (t, 1H), 7.71 (t, 1H), 7.82 (d, 1H), 8.00 (d, 1H), 8.19 (d, 1H); HPLC-MS (Method A): *m/z* = 279 (M+H); *R*<sub>t</sub> = 3.91 min.

#### Example 249

##### Methyl-phenyl-carbamic acid isoquinolin-3-yl ester

A solution of 3-hydroxyisoquinoline (0.44 g, 3.00 mmol), 1-methyl-3-(methyl-phenyl-carbamoyl)-3*H*-imidazol-1-ium iodide (1.03 g, 3.00 mmol) and triethylamine (0.42 ml, 3.00 mmol) in acetonitrile (15 ml) was stirred at room temperature for 18 hours. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane (50:50)) yielding the title compound (0.82 g, 99% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 3.49 (br.s, 3H), 7.24 (m, 1H), 7.33-7.47 (m, 5H), 7.51 (t, 1H), 7.63 (t, 1H), 7.77 (d, 1H), 7.94 (d, 1H), 9.06 (s, 1H); HPLC-MS (Method A): *m/z* = 279 (M+H); R<sub>t</sub> = 3.68 min.

#### Example 250

Methyl-phenyl-carbamic acid 4-trifluoromethyl-pyrimidin-2-yl ester

A solution of 4-(trifluoromethyl)-2-pyrimidol (0.49 g, 3.00 mmol), 1-methyl-3-(methyl-phenyl-carbamoyl)-3*H*-imidazol-1-ium iodide (1.03 g, 3.00 mmol) and triethylamine (0.42 ml, 3.00 mmol) in acetonitrile (15 ml) was stirred at room temperature for 3 days. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane (30:70)) yielding the title compound (0.35 g, 39% yield) as a colourless oil.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 3.45 (br.s, 3H), 7.28 (m, 1H), 7.38 (m, 4H), 7.52 (br.s, 1H), 8.93 (br.s, 1H); HPLC-MS (Method A): *m/z* = 320 (M+Na); R<sub>t</sub> = 3.58 min.

#### Example 251

Morpholine-4-carboxylic acid 4-trifluoromethyl-pyrimidin-2-yl ester

A solution of 4-(trifluoromethyl)-2-pyrimidol (0.49 g, 3.00 mmol), 4-morpholinecarbonyl chloride (0.45 g, 3.00 mmol) and 1,4-diazabicyclo[2.2.2]octane (0.51 g, 3.00 mmol) in *N,N*-dimethylformamide (15 ml) was stirred at room temperature for 2 hours. Water was added and the solution was extracted twice with dichloromethane. The combined organic layers were dried over sodium sulphate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane (30:70 → 50:50)) yielding the title compound (0.66 g, 80% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 3.57-3.81 (m, 8H), 7.57 (d, 1H), 8.97 (d, 1H).; HPLC-MS (Method A): *m/z* = 300 (M+Na); R<sub>t</sub> = 2.36 min.

**Example 252****Methyl-phenyl-carbamic acid 3-nitro-pyridin-2-yl ester**

A solution of 2-hydroxy-3-nitropyridine (0.42 g, 3.00 mmol), 1-methyl-3-(methyl-phenyl-carbamoyl)-3H-imidazol-1-ium iodide (1.03 g, 3.00 mmol) and triethylamine (0.42 ml, 3.00 mmol) in acetonitrile (15 ml) was stirred at room temperature for 3 days. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane (40:60)) yielding the title compound (0.41 g, 50% yield) as a yellow solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 3.41 + 3.58 (2 x br.s, 3H), 7.30 (m, 1H), 7.42 (m, 5H), 8.45 (br.d, 1H), 8.49 (br.s, 1H); HPLC-MS (Method A): *m/z* = 296 (M+Na); R<sub>t</sub> = 3.22 min.

**Example 253****Methyl-phenyl-carbamic acid 5-chloro-pyridin-2-yl ester**

A solution of 5-chloro-2-pyridol (0.39 g, 3.00 mmol), 1-methyl-3-(methyl-phenyl-carbamoyl)-3H-imidazol-1-ium iodide (1.03 g, 3.00 mmol) and triethylamine (0.42 ml, 3.00 mmol) in acetonitrile (15 ml) was stirred at room temperature for 3 days. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane (30:70)) yielding the title compound (0.78 g, 99% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 3.44 (br.s, 3H), 7.00 (br.s, 1H), 7.27 (m, 1H), 7.39 (m, 4H), 7.69 (d, 1H), 8.30 (d, 1H); HPLC-MS (Method A): *m/z* = 285 (M+Na); R<sub>t</sub> = 3.47 min.

**Example 254****Methyl-phenyl-carbamic acid 5-(2-nitro-phenyl)-pyrimidin-2-yl ester**

A solution of 5-(2-nitrophenyl)-pyrimidin-2-ol (0.35 g, 1.61 mmol), 1-methyl-3-(methyl-phenyl-carbamoyl)-3H-imidazol-1-ium iodide (0.55 g, 1.61 mmol) and triethylamine (0.22 ml, 1.61 mmol) in acetonitrile (15 ml) was heated at 50 °C for 18 hours. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane (50:50)) yielding the title compound (0.18 g, 32% yield) as a yellow oil.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 3.47 (br.s, 3H), 7.29 (m, 1H), 7.40 (m, 5H), 7.63 (dt, 1H), 7.72 (dt, 1H), 8.10 (d, 1H), 8.61 (br.s, 2H); HPLC-MS (Method A): *m/z* = 351 (M+H), 373 (M+Na), 723 (2M+Na); R<sub>t</sub> = 3.65 min.

**Example 255**

Methyl-phenyl-carbamic acid 5-trifluoromethyl-pyridin-2-yl ester

A solution of 2-hydroxy-5-(trifluoromethyl)pyridine (0.49 g, 3.00 mmol), 1-methyl-3-(methyl-phenyl-carbamoyl)-3*H*-imidazol-1-ium iodide (1.03 g, 3.00 mmol) and triethylamine (0.42 ml, 3.00 mmol) in acetonitrile (15 ml) was stirred at room temperature for 18 hours. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane (15:85)) yielding the title compound (0.59 g, 66% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 3.43 (br.s, 3H), 7.23 (br.s, 1H), 7.28 (m, 1H), 7.37 (m, 4H), 7.94 (br.d, 1H), 8.62 (br.s, 1H); HPLC-MS (Method A): *m/z* = 319 (M+Na); R<sub>t</sub> = 3.85 min.

**Example 256**

Methyl-phenyl-carbamic acid 3-chloro-5-trifluoromethyl-pyridin-2-yl ester

A solution of 3-chloro-5-(trifluoromethyl)-2-pyridinol (0.59 g, 3.00 mmol), 1-methyl-3-(methyl-phenyl-carbamoyl)-3*H*-imidazol-1-ium iodide (1.03 g, 3.00 mmol) and triethylamine (0.42 ml, 3.00 mmol) in acetonitrile (15 ml) was stirred at room temperature for 18 hours. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane (15:85)) yielding the title compound (146 mg, 15% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 3.43 (br.s, 3H), 7.30 (m, 1H), 7.40 (d, 4H), 8.00 (br.s, 1H), 8.52 (br.s, 1H); HPLC-MS (Method A): *m/z* = 353 (M+Na); R<sub>t</sub> = 4.29 min.

**Example 257**

Methyl-phenyl-carbamic acid 5-nitro-3-trifluoromethyl-pyridin-2-yl ester

A solution of 2-hydroxy-5-nitro-3-(trifluoromethyl)pyridine (0.36 g, 1.73 mmol), *N*-methyl-*N*-phenylcarbonyl chloride (0.44 g, 2.59 mmol) and 1,4-diazabicyclo[2.2.2]octane (0.29 g, 2.59 mmol) in tetrahydrofuran (15 ml) was stirred at room temperature for 18 hours. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane (15:85)) yielding the title compound (0.55 g, 92% yield) as an orange solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 3.46 (br.s, 3H), 7.23-7.46 (m, 5H), 8.70 (br.s, 1H), 9.37 (br.s, 1H); HPLC-MS (Method A): *m/z* = 364 (M+H); R<sub>t</sub> = 4.08 min.

**Example 258**

(3-Chloro-phenyl)-methyl-carbamic acid 4-trifluoromethyl-pyrimidin-2-yl ester

- 5 At 0 °C diphosgene (0.99 g, 5.00 mmol) was added to a stirred solution of 4-trifluoromethyl-2-hydroxypyrimidine (1.64 g, 10.0 mmol) in tetrahydrofuran (25 ml). The cooling bath was removed and stirring was continued at room temperature for 1 hour. (3-Chlorophenyl)-methylamine (0.35 g, 2.50 mmol) was added to one-fourth of the solution. After stirring overnight at room temperature the solvent was evaporated *in vacuo* and the residue was purified  
10 by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane (20:80)) followed by preparative HPLC, yielding the title compound (332 mg, 40%) as a colourless oil.  
<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 3.45 (br.s, 3H), 7.23-7.44 (m, 4H), 7.56 (d, 1H), 8.94 (d, 1H);  
HPLC-MS (Method A): *m/z* = 354 (M+H); *R<sub>t</sub>* = 4.03 min.

15 **Example 259**

Methyl-*m*-tolyl-carbamic acid 4-trifluoromethyl-pyrimidin-2-yl ester

- At 0 °C diphosgene (0.99 g, 5.00 mmol) was added to a stirred solution of 4-trifluoromethyl-2-hydroxypyrimidine (1.64 g, 10.0 mmol) in tetrahydrofuran (25 ml). The cooling bath was removed and stirring was continued at room temperature for 1 hour. Methyl-*m*-tolyl-amine (0.30  
20 g, 2.50 mmol) was added to one-fourth of the solution. After stirring overnight at room temperature the solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane (20:80)) followed by preparative HPLC, yielding the title compound (51 mg, 7%) as a colourless oil.  
25 <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 2.37 (s, 3H), 3.42 (br.s, 3H), 7.07-7.31 (m, 4H), 7.52 (br.s, 1H), 8.92 (br.s, 1H); HPLC-MS (Method A): *m/z* = 334 (M+Na); *R<sub>t</sub>* = 3.92 min.

**Example 260**

Morpholine-4-carboxylic acid 4-trifluoromethyl-pyrimidin-2-yl ester

- 30 A solution of 4-trifluoromethyl-2-hydroxypyrimidine (0.49 g, 3.00 mmol), 4-morpholinecarbonyl chloride (0.45 g, 3.00 mmol) and 1,4-diazabicyclo[2.2.2]octane (0.34 g, 3.00 mmol) in dimethylformamide (15 ml) was stirred at room temperature for 1 hour. Water and brine were added and the solution was extracted twice with dichloromethane. The combined organic layers were dried over sodium sulphate, filtered and evaporated *in vacuo*. The  
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residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane (30:70 → 50:50)) yielding the title compound (0.66 g, 80% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 3.45 (br.s, 3H), 7.23-7.44 (m, 4H), 7.56 (d, 1H), 8.94 (d, 1H);

HPLC-MS (Method A): *m/z* = 354 (M+H); R<sub>t</sub> = 4.03 min.

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#### Example 261

Methyl-phenyl-carbamic acid 4,5-dichloro-pyridazin-3-yl ester

A solution of 4,5-dichloro-3-hydroxypyridazine (0.49 g, 3.00 mmol), *N*-methyl-*N*-phenylcarbonyl chloride (0.51 g, 3.00 mmol) and triethylamine (0.42 ml, 3.00 mmol) in tetrahydrofuran (15 ml) was stirred at room temperature for 3 days. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane (20:80)) yielding the title compound (0.12 g, 14% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 3.50 (s, 3H), 7.18-7.32 (m, 5H), 7.63 (s, 1H); HPLC-MS

(Method A): *m/z* = 320 (M+Na); R<sub>t</sub> = 2.91 min.

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#### Example 262

Methyl-phenyl-carbamic acid 5-benzoylamino-pyridin-2-yl ester

A solution of *N*-(6-hydroxy-pyridin-3-yl)-benzamide (0.64 g, 3.00 mmol), *N*-methyl-*N*-phenylcarbonyl chloride (0.51 g, 3.00 mmol) and 1,4-diazabicyclo[2.2.2]octane (0.34 g, 3.00 mmol) in dimethylformamide (15 ml) was stirred at room temperature for 1 hour. Water was added and the precipitates were collected by suction. The solids were dissolved in dichloromethane and the solution was dried over sodium sulphate, filtered and evaporated *in vacuo*. The residue was dissolved in ethyl acetate and filtered over a short pad of silica. Evaporation of the solvent *in vacuo* yielded the title compound (0.70 g, 68% yield) as a thick oil.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 3.40 (br.s, 3H), 6.90 (br.s, 1H), 7.26 (m, 1H), 7.31-7.44 (m, 6H), 7.50 (m, 1H), 7.88 (d, 2H), 8.08 (dd, 1H), 8.37 (d, 1H), 8.79 (br.s, 1H); HPLC-MS (Method A):

*m/z* = 348 (M+H); R<sub>t</sub> = 3.49 min.

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25  
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#### Example 263

Methyl-phenyl-carbamic acid 5-(cyclohexanecarbonyl-amino)-pyridin-2-yl ester

A solution of cyclohexanecarboxylic acid (6-hydroxy-pyridin-3-yl)-amide (0.66 g, 3.00 mmol),

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*N*-methyl-*N*-phenylcarbamoyl chloride (0.51 g, 3.00 mmol) and 1,4-diazabicyclo[2.2.2]octane (0.34 g, 3.00 mmol) in dimethylformamide (20 ml) was stirred at room temperature for 18 hours. Water was added and the precipitates were collected by suction. The solids were dissolved in dichloromethane and the solution was dried over sodium sulphate, filtered and evaporated *in vacuo*. The residue was crystallised from ethyl acetate:heptane yielding the title compound (0.75 g, 71% yield) as a slightly coloured solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 1.18-1.33 (m, 3H), 1.42-1.59 (m, 2H), 1.60 (m, 1H), 1.77-1.94 (m, 4H), 2.20 (m, 1H), 3.45 (br.s, 3H), 6.91 (br.s, 1H), 7.28 (m, 1H), 7.39 (m, 4H), 7.94 (br.s, 1H), 8.00 (dd, 1H), 8.20 (d, 1H); HPLC-MS (Method A): *m/z* = 354 (M+H); *R*<sub>t</sub> = 3.74 min.

#### Example 264

Methyl-phenyl-carbamic acid 4,4-dimethyl-2,6-dioxo-3,4,5,6-tetrahydro-2*H*-[1,3']bipyridinyl-6'-yl ester

A solution of 6'-hydroxy-4,4-dimethyl-4,5-dihydro-3*H*-[1,3']bipyridinyl-2,6-dione (0.70 g, 3.00 mmol), *N*-methyl-*N*-phenylcarbamoyl chloride (0.51 g, 3.00 mmol) and 1,4-diazabicyclo[2.2.2]octane (0.34 g, 3.00 mmol) in dimethylformamide (20 ml) was stirred at room temperature for 18 hours. Water was added and the precipitates were collected by suction and subsequently dried in a vacuum oven yielding the title compound (0.75 g, 71% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 1.20 (s, 6H), 2.68 (s, 4H), 3.44 (br.s, 3H), 7.14 (br.s, 1H), 7.25 (m, 1H), 7.37 (m, 4H), 7.48 (br.d, 1H), 8.08 (d, 1H); HPLC-MS (Method A): *m/z* = 368 (M+H); *R*<sub>t</sub> = 3.41 min.

#### Example 265

Methyl-phenyl-carbamic acid 5-(2,2-dimethyl-propionylamino)-pyridin-2-yl ester

A solution of *N*-(6-hydroxy-pyridin-3-yl)-2,2-dimethyl-propionamide (0.58 g, 3.00 mmol), *N*-methyl-*N*-phenylcarbamoyl chloride (0.51 g, 3.00 mmol) and 1,4-diazabicyclo[2.2.2]octane (0.34 g, 3.00 mmol) in dimethylformamide (20 ml) was stirred at room temperature for 1 hour. Water was added and a thick oil was being formed. The water was decanted and the residue was dissolved in dichloromethane. The solution was dried over sodium sulphate, filtered and evaporated *in vacuo* yielding the title compound (0.55 g, 56% yield) as a brown oil that solidified upon standing.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 1.29 (s, 9H), 3.43 (br.s, 3H), 6.97 (br.s, 1H), 7.26 (m, 1H), 7.38



(m, 4H), 7.64 (br.s, 1H), 8.10 (dd, 1H), 8.28 (br.s, 1H); HPLC-MS (Method A):  $m/z$  = 348 (M+H);  $R_t$  = 3.49 min.

#### Example 266

##### 5 Methyl-phenyl-carbamic acid 5-(2-cyclohexyl-acetylamino)-pyridin-2-yl ester

A solution of 2-cyclohexyl-*N*-(6-hydroxy-pyridin-3-yl)-acetamide (0.70 g, 3.00 mmol), *N*-methyl-*N*-phenylcarbamoyl chloride (0.51 g, 3.00 mmol) and 1,4-diazabicyclo[2.2.2]octane (0.34 g, 3.00 mmol) in dimethylformamide (15 ml) was stirred at room temperature for 1 hour.

10 Water was added and the precipitates were collected by suction. The solids were dissolved in dichloromethane and the solution was dried over sodium sulphate, filtered and evaporated *in vacuo*. The residue was crystallised from ethyl acetate:heptane yielding the title compound (0.79 g, 72% yield) as a brown solid.

$^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ ):  $\delta$  0.86-1.01 (m, 2H), 1.05-1.37 (m, 3H), 1.60-1.78 (m, 5H), 1.83  
15 (m, 1H), 2.13 (d, 2H), 3.46 (br.s, 3H), 6.90 (br.s, 1H), 7.27 (m, 1H), 7.39 (m, 4H), 7.98 (d, 1H), 8.12 (s + br.s, 2H, CH + NH); HPLC-MS (Method A):  $m/z$  = 368 (M+H);  $R_t$  = 4.04 min.

#### Example 267

##### 20 Methyl-phenyl-carbamic acid 5-(4-methoxy-phenoxy)-pyrimidin-2-yl ester

A solution of 5-(4-methoxy-phenoxy)-pyrimidin-2-ol (0.44 g, 2.00 mmol), *N*-methyl-*N*-phenylcarbamoyl chloride (0.34 g, 2.00 mmol) and 1,4-diazabicyclo[2.2.2]octane (0.22 g, 2.00 mmol) in dimethylformamide (15 ml) was stirred at room temperature for 1 hour. Water  
25 was added and the precipitates were collected by suction. The solids were dissolved in dichloromethane and the solution was dried over sodium sulphate, filtered and evaporated *in vacuo*. The residue was crystallised from ethyl acetate:heptane yielding the title compound (0.55 g, 79% yield) as an off-white solid.

$^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ ):  $\delta$  3.43 (br.s, 3H), 3.82 (s, 3H), 6.91 + 7.00 (AB-system, 2 x 2H),  
7.26 (m, 1H), 6.39 (m, 4H), 8.33 (s, 2H); HPLC-MS (Method A):  $m/z$  = 352 (M+H);  $R_t$  = 4.02  
30 min.

#### Example 268

##### Methyl-phenyl-carbamic acid 5-(3,4-dichloro-phenoxy)-pyrimidin-2-yl ester

35 A solution of 5-(3,4-dichloro-phenoxy)-pyrimidin-2-ol (0.51 g, 2.00 mmol), *N*-methyl-*N*-

phenylcarbamoyl chloride (0.34 g, 2.00 mmol) and 1,4-diazabicyclo[2.2.2]octane (0.22 g, 2.00 mmol) in dimethylformamide (15 ml) was stirred at room temperature for 1 hour. Water was added and the precipitates were collected by suction. The solids were dissolved in dichloromethane and the solution was dried over sodium sulphate, filtered and evaporated *in vacuo*. The residue was crystallised from ethyl acetate:heptane yielding the title compound (0.51 g, 65% yield) as an off-white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 3.44 (br.s, 3H), 6.89 (dd, 1H), 7.14 (d, 1H), 7.27 (m, 1H), 7.39 (m, 4H), 7.44 (d, 1H), 8.42 (s, 2H); HPLC-MS (Method A): *m/z* = 390 (M+H); *R<sub>t</sub>* = 4.66 min.

#### 10 Example 269

Methyl-phenyl-carbamic acid 6-pyridin-2-ylmethyl-pyridazin-3-yl ester

A solution of 6-(2-pyridinylmethyl)-3-pyridazinol (100 mg, 0.53 mmol), *N*-methyl-*N*-phenylcarbamoyl chloride (91 mg, 0.53 mmol) and 1,4-diazabicyclo[2.2.2]octane (60 mg, 0.53 mmol) in dimethylformamide (10 ml) was stirred at room temperature for 2 hours. Water was added and the solution was extracted twice with dichloromethane. The combined organic layers were dried over sodium sulphate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate) yielding the title compound (70 mg, 41% yield) as a yellow oil.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 3.42 (br.s, 3H), 4.50 (s, 2H), 7.11-7.33 (m, 4H), 7.39 (d, 4H), 7.60 (m, 2H), 8.52 (d, 1H); HPLC-MS (Method A): *m/z* = 321 (M+H); *R<sub>t</sub>* = 1.98 min.

#### Example 270

Methyl-phenyl-carbamic acid 6-(4-methoxy-benzyl)-pyridazin-3-yl ester

A solution of 6-(2-pyridinylmethyl)-3-pyridazinol (97 mg, 0.45 mmol), *N*-methyl-*N*-phenylcarbamoyl chloride (76 mg, 0.45 mmol) and 1,4-diazabicyclo[2.2.2]octane (50 mg, 0.45 mmol) in dimethylformamide (10 ml) was stirred at room temperature for 2 hours. Water was added and the solution was extracted twice with dichloromethane. The combined organic layers were dried over sodium sulphate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane (50:50)) yielding the title compound (117 mg, 41% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 3.43 (br.s, 3H), 3.79 (s, 3H), 4.28 (s, 2H), 6.83 (d, 2H), 7.17 (d, 2H), 7.27 (m, 3H), 7.40 (d, 4H); HPLC-MS (Method A): *m/z* = 350 (M+H); *R<sub>t</sub>* = 3.60 min.

**Example 271**

Methyl-phenyl-carbamic acid 6-(2,4-dichloro-benzyl)-pyridazin-3-yl ester

A solution of 6-(2,4-dichlorobenzyl)-3-pyridazinol (98 mg, 0.38 mmol), *N*-methyl-*N*-phenylcarbonyl chloride (65 mg, 0.38 mmol) and 1,4-diazabicyclo[2.2.2]octane (43 mg, 0.38 mmol) in dimethylformamide (10 ml) was stirred at room temperature for 2 hours. Water was added and the solution was extracted twice with dichloromethane. The combined organic layers were dried over sodium sulphate, filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane (40:60)) yielding the title compound (119 mg, 80% yield) as a yellow oil.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 3.43 (br.s, 3H), 4.42 (s, 2H), 7.17-7.44 (m, 10H); HPLC-MS (Method A): *m/z* = 388 (M+H); R<sub>t</sub> = 4.44 min.

**Example 272 (General procedure 15)**

4-Pyridin-2-yl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)phenyl chloroformate and 1-pyridin-2-yl-piperazine. White crystals, yield 87 %; m.p. 247 - 248 °C; HPLC-MS: *m/z* = 445 (M+H); IR (KBr): ν 1713 (C=O) cm<sup>-1</sup>.

**Example 273 (General procedure 15)**

4-(1,3-Benzodioxol-5-yl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(1,3-benzodioxol-5-yl)-piperazine. The crude product was partitioned between dichloromethane and 1 M aqueous sodium carbonate. The organic layer was washed with water, dried and evaporated. The residue was triturated with ethyl acetate - heptane (1:4) and the precipitate was collected by filtration and dried to give the title compound. Yield 39 %; m.p. 146 - 147 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.60 - 8.56 (br, 1H), 8.29 - 8.20 (dd-like, 1H), 7.31 - 7.20 (m, 5H), 6.84 - 6.72 (d-like, 1H), 6.76 - 6.72 (d-like, 1H), 6.45 - 6.36 (dd-like, 1H), 3.81 - 3.47 (br m, 4H), 3.16 - 3.00 (br,m, 4H); HPLC-MS: *m/z* = 488 (M+H); IR (KBr): ν 1719 (C=O) cm<sup>-1</sup>.

**Example 274 (General procedure 15)**

4-[2-(2-Hydroxyethoxy)ethyl]-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 2-(2-hydroxyethoxy)ethyl-piperazine. Yield 13 %; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 10.8 (br), 8.61 - 8.54 (br, 1H), 8.30 - 8.21 (dd-like, 1H), 7.32 - 7.19 (m, 5H), 4.3 - 3.9 (br, 2H), 3.9 - 3.0 (br m, alicyclics and aliphatics + water); HPLC-MS: m/z = 456(M+H); IR (KBr): ν 1724 (C=O) cm<sup>-1</sup>.

10 **Example 275** (General procedure 15)

4-(Diphenylmethyl)piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(diphenylmethyl)piperazine, white crystals, yield 74 %; m.p. 168 - 169 °C;

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 12.4 (br, 1H), 8.60 - 8.54 (d-like m, 1H), 8.28 - 8.20 (dd-like m, 1H), 7.98 - 7.82 (br, 2H), 7.55 - 7.15 (br m, 13 H), 5.6 (br, 1H), 4.35 - 3.48 (br, 3H), 3.35 - 3.0 (br, 5H); IR (KBr): ν 1723 (C=O) cm<sup>-1</sup>.

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**Example 276** (General procedure 15)

4-(4-*tert*-Butylbenzyl)piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)phenyl ester

25 The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(4-*tert*-butylbenzyl)diphenylmethyl)piperazine, white crystals, yield 56 %; m.p. 274 - 275 °C; HPLC-MS: m/z = 514 (M+H); IR (KBr): ν 1721 (C=O) cm<sup>-1</sup>.

30 **Example 277** (General procedure 15)

4-(4-Fluorobenzyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(4-fluorobenzyl)piperazine, white crystals, yield 69 %;

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m.p. 240 - 243 °C; HPLC-MS: m/z = 476 (M+H), 498 (M+Na); IR (KBr):  $\nu$  1720 (C=O)  $\text{cm}^{-1}$ .

**Example 278** (General procedure 15)

5 4-(2-Thienylethyl)piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(2-thienylethyl)piperazine, white crystals, yield 62 %; m.p. 236 - 237 °C;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  11.51 (br s, 1H), 8.61 - 8.54 (br m, 1H), 7.48 - 7.17 (m, 6H), 7.06 - 6.89 (m, 2H), 4.4 - 3.9 (br, 2H), 3.9 - 2.6 (br m, 16.5 H ~ 12H + water); HPLC-MS: m/z = 478 (M+H); IR (KBr):  $\nu$  1714 (C=O)  $\text{cm}^{-1}$ .

**Example 279** (General procedure 15)

15 4-(1-Phenylethyl)piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)phenyl ester

The crude hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(1-phenylethyl)piperazine. Trituration with water, filtering and drying of the residue gave white crystals, yield 31 %; m.p. 242 °C;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  11.56 (br s, 1H), 8.61 - 8.52 (br m, 1H), 8.30 - 8.19 (dd-like m, 1H), 7.77 - 7.31 (br m, 5H), 7.31 - 7.13 (m, 5H), 4.60 - 3.27 (br m, 6H + water), 3.27 - 2.57 (br, 3H), 1.73 (br d, 3H); IR (KBr):  $\nu$  1712 (C=O)  $\text{cm}^{-1}$ .

**Example 280** (General procedure 15)

25 4-Octylpiperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)phenyl ester

The crude hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(1-phenylethyl)piperazine. Trituration with water, filtering and drying of the residue gave white crystals, yield 31 %; m.p. 244-245 °C;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  11.16 (br s, 1H), 8.61 - 8.57 (br m, 1H), 8.30 - 8.20 (dd-like m, 1H), 7.32 - 7.18 (m, 5H), 4.39 - 3.96 (br, 2H), 3.77 - 3.38 (br, 4H), 3.25 - 2.88 (br, 4H), 1.84 - 1.58 (br, 2H), 1.42 - 1.12 (br s, 10H), 0.87 (br t, 3H); IR (KBr):  $\nu$  1731, 1713 (C=O)  $\text{cm}^{-1}$ .

**Example 281** (General procedure 15)

35 4-(3-Dimethylamino-propyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-

phenyl ester

The crude hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(3-dimethylaminopropyl)piperazine. A suspension of the product in ether was stirred with an excess of HCl in ether and the precipitate was washed with ether and dried to give the dihydrochloride of the title compound as white crystals, m.p. 292 - 293 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 11.35 (br s, 1H), 10.46 (br s, 1H), 8.61 - 8.52 (br m, 1H), 8.31 - 8.17 (m, 1H), 7.35 - 7.16 (m, 5H), 4.45 - 4.00 (br, 2H), 3.80 - 3.45 (br, 4H), 3.30 - 3.01 (br, 6H), 2.78 (br s, 6H), 2.31 - 2.07 (br, 2H); IR (KBr): ν 1731, 1713 (C=O) cm<sup>-1</sup>.

**Example 282** (General procedure 15)

4-Pyrimidin-2-yl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(pyrimidin-2-yl)piperazine. The crude product was dried in vacuo at 50 °C for 80 min and extracted with ether. The ether phase was evaporated and the residue was purified by flash chromatography on silica eluted with ethyl acetate - heptane 1:1 to give the title compound as white needles. Yield 14 %; m.p. 120-121 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.61 - 8.56 (br, 1H), 8.41 (d, J = 4.8 Hz, 2H), 8.29 - 8.20 (dd-like, 1H), 7.31 - 7.20 (m, 5H), 6.69 (t-like m, J ~ 4.8 Hz, 1H), 3.94 - 3.78 (br s, 4H), 3.78 - 3.45 (br d, 4H); HPLC-MS: m/z = 446 (M+H); IR (KBr): ν 1719 (C=O) cm<sup>-1</sup>.

**Example 283** (General procedure 15)

4-Cyclopropylmethyl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-cyclopropylpiperazine, yield 62 %. Recrystallisation from 0.2 M HCl gave white crystals, m.p. 238 - 239 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 11.51 (br s, 1H), 8.61 - 8.55 (m, 1H), 8.30 - 8.20 (m, dd, 1H), 7.32 - 7.19 (m, d+s, 5H), 4.44 - 4.00 (br, 2H), 3.80 - 3.40 (br m, 4H), 3.29 - 2.93 (br m, 4H), 1.28 - 1.05 (br m, 1H), 0.75 - 0.58 (m, 2H), 0.50 - 0.35 (m, 2H). IR (KBr): ν 1730, 1713 (C=O) cm<sup>-1</sup>.

**Example 284** (General procedure 15)

4-Methyl-1,4-diazepane-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-methylhomopiperazine; white crystals, m.p. 210 - 211 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 11.27 (br s, 1H), 8.61 - 8.54 (m, 1H), 8.30 - 8.20 (dd-like m, 1H), 7.34 - 7.18 (m, 5H), 4.13 - 3.08 (br, 11H, 8H + water), 2.80 (br s, 3H), 2.47 - 1.98 (br m, 2H); IR (KBr): ν 1723, 1711 (C=O) cm<sup>-1</sup>.

**Example 285** (General procedure 15)

4-Phenethyl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

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The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-phenethylpiperazine, yield 54 %. Recrystallisation from 99% EtOH gave white crystals, m.p. 245 - 247 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 11.72 (br, 1H), 8.63 - 8.53 (br, 1H), 8.31 - 8.19 (dd-like m, 1H), 7.44 - 7.16 (m, 10H), 4.44 - 4.01 (br, 2H), 3.83 - 3.45 (br, 4H), 3.45 - 2.95 (br, ~8H, 6H + water); IR (KBr): ν 1713 (C=O) cm<sup>-1</sup>.

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**Example 286** (General procedure 15)

4-Pyridin-2-ylmethyl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

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The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-pyridin-2-ylmethyl-piperazine. White crystals, yield 64 %; m.p. 189 - 190 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.72 - 8.63 (m, 1H), 8.60 - 8.55 (br, 1H), 8.29 - 8.20 (dd-like, 1H), 8.02 - 7.90 (m, 1H), 7.80 - 7.65 (m, 1H), 7.56 - 7.45 (m, 1H), 7.31 - 7.22 (m, 5H), 4.52 (br s, 2H), 4.06 - 3.68 (br s, 4H), 3.68 - 2.93 (br, 4H + NH + water); HPLC-MS: m/z = 459 (M+H); IR (KBr): ν 1717 (C=O) cm<sup>-1</sup>.

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**Example 287** (General procedure 15)

4-Pyridin-3-ylmethyl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

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The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-pyridin-3-ylmethyl-piperazine. Trituration with water, filtering and drying of the residue gave white crystals. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.78 - 8.51 (m, 3H), 8.30 - 8.18 (dd-like, 1H), 8.12 - 8.00 (br d, 1H), 7.57 - 7.46 (m, 1H), 7.32 - 7.17 (m, 5H), 4.65

35

- 4.11 (br, 2H), 4.11 - 2.78 (br m, 6H + water); HPLC-MS:  $m/z = 459$  (M+H); IR (KBr):  $\nu$  1723 (C=O)  $\text{cm}^{-1}$ .

**Example 288** (General procedure 15)

5 4-(3-Phenylpropyl)piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(3-phenylpropyl)piperazine, yield 68 %. m.p. 235 - 238  
10 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  11.51 (br, 1H), 8.61 - 8.55 (br, 1H), 8.29 - 8.20 (dd-like m, 1H), 7.38 - 7.16 (m, 10H), 4.38 - 3.96 (br, 2H), 3.83 - 3.40 (br, 4H), 3.30 - 2.91 (br, 4H), 2.75 - 2.57 (t-like m, 2H), 2.20 - 1.94 (m, 2H); IR (KBr):  $\nu$  1715 (C=O)  $\text{cm}^{-1}$ .

**Example 289** (General procedure 15)

15 4-(4-Phenylbutyl)piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(4-phenylbutyl)piperazine, yield 71 %. m.p. 232 - 234 °C;  
20  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  11.32 (br s, 1H), 8.61 - 8.55 (br, 1H), 8.29 - 8.20 (dd-like m, 1H), 7.36 - 7.13 (m, 10H), 4.40 - 3.97 (br, 2H), 3.81 - 3.39 (br m, 4H), 3.26 - 2.91 (br, 4H), 2.71 - 2.55 (t-like m, 2H), 1.88 - 1.51 (br m, 4H); IR (KBr):  $\nu$  1728, 1713 (C=O)  $\text{cm}^{-1}$ .

25 **Example 290** (General procedure 15)

4-Benzyl-1,4-diazepane-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-benzylhomopiperazine, crude yield 70 %. 0.20 g Of the  
30 crude product was heated with 3 ml of water, cooled at 0 °C, the precipitate filtered off and dried; m.p. 231 - 233 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  11.38 (br s, 1H), 8.62 - 8.55 (br, 1H), 8.30 - 8.20 (dd-like m, 1H), 7.76 - 7.60 (br, 2H), 7.52 - 7.41 (br m, 3H), 7.32 - 7.19 (m, 5H), 4.38 (br s, 2H), 4.18 - 3.01 (br m, 8H + water), 2.6 - 2.0 (br, 2H + DMSO); IR (KBr):  $\nu$  1726, 1710 (C=O)  $\text{cm}^{-1}$ .



**Example 291** (General procedure 15)

4-(3,4-Dichlorophenyl)piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)phenyl ester

- 5 The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(3,4-dichlorophenyl)piperazine. The crude product was partitioned between dichloromethane and 2 M aqueous sodium carbonate. The organic layer was washed with water, dried and evaporated. The residue was triturated with ethyl acetate - heptane (1:4) and the precipitate was collected by filtration and dried to give the title
- 10 compound as white crystals. Yield 28 %; m.p. 115 - 116 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.61 - 8.55 (br, 1H), 8.30 - 8.20 (dd-like, 1H), 7.48 - 7.40 (d-like, 1H), 7.31 - 7.16 (m, 6H), 7.04 - 6.94 (dd-like, 1H), 3.83 - 3.47 (br m, 4H), 3.36 - 3.24 (br s, 4H + water); HPLC-MS: m/z = 512 (M+H); IR (KBr): ν 1724, 1706 cm<sup>-1</sup>.

15 **Example 292** (General procedure 15)

4-(4-Fluorophenyl)piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)phenyl ester

- The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(4-fluorophenyl)piperazine. White crystals, yield 20 %;
- 20 m.p. 131-132 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.61 - 8.53 (br, 1H), 8.30 - 8.19 (dd-like, 1H), 7.33 - 7.17 (m, 5H), 7.17 - 6.95 (m, 4H), 3.85 - 3.47 (br d, 4H), 3.25 - 3.07 (br m, 4H); HPLC-MS: m/z = 462 (M+H); IR (KBr): ν 1739, 1714 cm<sup>-1</sup>.

25 **Example 293** (General procedure 15)

4-(2-Chlorophenyl)piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)phenyl ester

- The the hydrochloride of title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(2-chlorophenyl)piperazine. Drying *in vacuo* at 50 °C for
- 30 3½ h gave the title compound; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.61 - 8.55 (br, 1H), 8.29 - 8.20 (dd-like, 1H), 7.53 - 7.41 (m, 1H), 7.39 - 7.17 (m, 7H), 7.14 - 7.03 (m, 1H), 4.58 (br s, NH + water), 3.85 - 3.55 (br m, 4H), 3.12 - 2.99 (br m, 4H); HPLC-MS: m/z = 478 (M+H); IR (KBr): ν 1733 (C=O) cm<sup>-1</sup>.

**Example 294** (General procedure 15)

(2-Dimethylamino-ethyl)methylcarbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

- 5 The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and N,N,N'-trimethylethylenediamine; m.p. 139 - 140 °C; <sup>1</sup>H NMR (MeOH-d<sub>6</sub>): δ 8.45 - 8.38 (br, 1H), 8.15 - 8.05 (dd-like m, 1H), 7.31 - 7.11 (m, 5H), 3.84 - 3.73 (br m, 2H), 3.54 - 3.38 (br m, 3H), 3.19 (br s, 2H), 2.99 (br s, 6H); traces of impurities at 3.9 (br) and 3.1 (br); IR (KBr): ν 2695, 1705 cm<sup>-1</sup> (C=O) cm<sup>-1</sup>.

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**Example 295** (General procedure 15)

4-Methylpiperazine-1-carboxylic acid 4-chlorophenyl ester

- The hydrochloride of the title compound was prepared from 4-chlorophenyl chloroformate and 1-methylpiperazine, yield 81 %. White crystals, m.p. 237 - 240 °C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 11.67 (br s, 1H), 7.50, 7.45, 7.24, 7.20 (AB-system, d = 7.47 and 7.22; J = 8.84 Hz, 4H), 4.40 - 3.91 (br, 2H), 3.77 - 2.92 (br m, 6H + water), 2.77 (s, 3H); IR (KBr): ν 1717 (C=O) cm<sup>-1</sup>.

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**Example 296** (General procedure 15)

- 20 4-(4-Phenylbutyl)piperazine-1-carboxylic acid 4-chlorophenyl ester

- The hydrochloride of the title compound was prepared from 4-chlorophenyl chloroformate and 1-(4-phenylbutyl)piperazine, yield 86 %. White crystals, m.p. 230 - 232 °C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 11.43 (br, 1H), 7.51 - 7.43 (d-like m, 2H), 7.33 - 7.15 (m, 7H), 4.33 - 3.95 (br, max at 4.21 and 4.10 ppm; 2H), 3.72 - 3.36 (br m, 4H), 3.22 - 2.96 (br, max at 3.10 ppm, 4H), 2.62 (t, J = 7.54 Hz, 2H), 1.84 - 1.69 (m, 2H), 1.69 - 1.54 (m, 2H) ppm; IR (KBr): ν 1736, 1720 (C=O) cm<sup>-1</sup>.

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**Example 297** (General procedure 15)

- 30 4-[2-(2-Hydroxyethoxy)ethyl]piperazine-1-carboxylic acid 4-(4-trifluoromethylphenoxy)phenyl ester

- The hydrochloride of the title compound was prepared from 4-(4-trifluoromethylphenoxy)phenyl chloroformate and 2-(2-hydroxyethoxy)ethyl-piperazine. Pale powder, m.p. 176 - 178 °C; <sup>1</sup>H NMR (MeOH-d<sub>4</sub>): δ Two AB-systems: 7.68 - 7.58 (d-like, 2H)

35

and 7.29 - 7.04 (m, 6H); 4.74 - 3.18 (complex, 16 H, partly overlapping with MeOH- $d_4$ ); HPLC-MS  $m/z$  = 455 (M+H), 477 (M+Na),  $R_t$  = 3.08 min.; IR (KBr):  $\nu$  1718 (C=O)  $\text{cm}^{-1}$ .

**Example 298** (General procedure 15)

5    4-(1-Ethylpropyl)piperazine-1-carboxylic acid 4-(4-trifluoromethylphenoxy)phenyl ester

The hydrochloride of the title compound was prepared from 4-(4-trifluoromethylphenoxy)phenyl chloroformate and 1-(1-ethylpropyl)piperazine, yield 74 %. White crystals,  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  10.59 (br s, 1H), 2 AB-systems: 7.81 - 7.70 (d-like, 2H) and 7.31 - 7.09 (m, 6H); 4.38 - 3.99 (br s, 2H), 3.90 - 3.38 (br, 4H), 3.33 - 2.99 (br, 3H), 2.01 - 1.77 (m, 2H), 1.77 - 1.49 (m, 2H), 0.98 (t, 6H); HPLC-MS  $m/z$  = 437 (M+H).

**Example 299** (General procedure 15)

15    4-Cycloheptylpiperazine-1-carboxylic acid 4-(4-trifluoromethylphenoxy)phenyl ester

The hydrochloride of the title compound was prepared from 4-(4-trifluoromethylphenoxy)phenyl chloroformate and 1-cycloheptylpiperazine. The crude product was partitioned between dichloromethane and aqueous sodium carbonate. The organic layer was washed with water, dried and evaporated. The residue was triturated with ethyl acetate - heptane (1:4) and the precipitate was collected by filtration and dried to give the title compound. White crystals,  $^1\text{H}$  NMR (MeOH- $d_4$ ):  $\delta$  Two AB-systems: 7.68 - 7.58 (d-like, 2H) and 7.23 - 7.04 (m, 6H); 3.86 - 3.50 (br d, 4H), 2.98 - 2.66 (br, 5H), 2.04 - 1.37 (m, 12H); HPLC-MS  $m/z$  = 463 (M+H); IR (KBr):  $\nu$  1730, 1707  $\text{cm}^{-1}$ .

25    **Example 300** (General procedure 15)

4-Cyclohexylpiperazine-1-carboxylic acid 4-(4-trifluoromethylphenoxy)phenyl ester

The hydrochloride of the title compound was prepared from 4-(4-trifluoromethylphenoxy)phenyl chloroformate and 1-cyclohexylpiperazine, yield 80 %. White crystals, m.p. 290 - 291  $^{\circ}\text{C}$ ,  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  10.82 (br s, 1H), 2 AB-systems: 7.83 - 7.69 (d-like, 2H) and 7.32 - 7.10 (m, 6H); 4.40 - 4.02 (br, 2H), 3.75 - 3.39 (br, 4H), 3.31 - 2.98 (br, 3H), 2.23 - 2.02 (m, 2H), 1.92 - 1.74 (m, 2H), 1.70 - 0.97 (m, 6H); HPLC-MS  $m/z$  = 449 (M+H); IR (KBr):  $\nu$  1717 (C=O)  $\text{cm}^{-1}$ .

35    **Example 301** (General procedure 15)

4-(4-Chlorobenzyl)piperazine-1-carboxylic acid 4-(4-trifluoromethylphenoxy)phenyl ester

The hydrochloride of the title compound was prepared from 4-(4-trifluoromethylphenoxy)phenyl chloroformate and 1-(4-chlorobenzyl)piperazine, yield 86 %.

- 5 White crystals, m.p. 232 - 234 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 11.92 (br s, 1H), 3 AB-systems: 7.83 - 7.62 (t-like, 4H) and 7.62 - 7.48 (d-like, 2H), and 7.32 - 7.07 (m, 6H); 4.51 - 3.95 (br s at 4.37 ppm overlapping with br signal at 4.2 ppm, 4H), 3.95 - 2.95 (br m, 9H: 6H + water); IR (KBr): ν 1717 (C=O) cm<sup>-1</sup>.

10 **Example 302** (General procedure 15)

4-(4-Methylbenzyl)piperazine-1-carboxylic acid 4-(4-trifluoromethylphenoxy)phenyl ester

- 15 The hydrochloride of the title compound was prepared from 4-(4-trifluoromethylphenoxy)phenyl chloroformate and 1-(4-methylbenzyl)piperazine, yield 96 %. White crystals, m.p. 250-252°C; HPLC-MS m/z = 472 (M+H); IR (KBr): ν 1720 (C=O) cm<sup>-1</sup>.

**Example 303** (General procedure 15)

- 20 4-(4-Methoxybenzyl)piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(4-methoxybenzyl)piperazine, yield 78 %. White crystals, m.p. 237 - 238 °C; HPLC-MS m/z = 488 (M+H); IR (KBr): ν 1719 (C=O) cm<sup>-1</sup>.

25

**Example 304** (General procedure 15)

4-(2-Chloro-6-fluoro-benzyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

- 30 The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(2-chloro-6-fluorobenzyl)piperazine. White crystals, m.p. 204 - 205 °C (from ethanol); HPLC-MS m/z = 510 (M+H); IR (KBr): ν 1726 (C=O) cm<sup>-1</sup>;

**Example 305** (General procedure 15)

- 35 4-(3-Methoxyphenyl)piperazine-1-carboxylic acid 4-(4-trifluoromethylphenoxy)phenyl ester

The hydrochloride of the title compound was prepared from 4-(4-trifluoromethylphenoxy)phenyl chloroformate and 1-(3-methoxyphenyl)piperazine. White crystals, m.p. 168-171°C (sinters at 160 °C); HPLC-MS  $m/z$  = 473(M+1); IR (KBr):  $\nu$  1739, 1716 (C=O)  $\text{cm}^{-1}$ .

**Example 306** (General procedure 15)

4-Benzyl-piperazine-1-carboxylic acid 4-(3-chloro-5-trifluoromethyl-pyridin-2-yloxy)phenyl ester

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The hydrochloride of the title compound was prepared from 4-(3-chloro-5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-benzyl-piperazine, yield 94 %. White crystals; m.p. 111 - 113 °C (resolidifies) and 114 - 115 °C; HPLC-MS  $m/z$  = 492 (M+H).

15 **Example 307** (General procedure 8)Methyl-phenyl-carbamic acid 4-iodo-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-4-iodopyrazole and N-methyl-N-phenylcarbonyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (98%, oil).

20  $^1\text{H}$  NMR (300MHz;  $\text{CDCl}_3$ ):  $\delta$  3.44 (bs, 3H), 7.30-7.48 (m, 7H).; HPLC-MS :  $m/z$  = 343.9 (M+1);  $R_t$  = 4.12 min.

**Example 308** (General procedure 8)Methyl-phenyl-carbamic acid benzotriazol-1-yl ester

25 The title compound was prepared from 1-hydroxybenzotriazole and N-methyl-N-phenylcarbonyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (98%, crystallizes slowly).

$^1\text{H}$  NMR (300MHz;  $\text{CDCl}_3$ ):  $\delta$  3.50 (bs, 3H), 7.37-7.57 (m, 8H), 8.04 (d, 1H).; HPLC-MS :  $m/z$  = 269.0 (M+1);  $R_t$  = 3.69 min.

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**Example 309** (General procedure 8)Methyl-phenyl-carbamic acid [1,2,3]triazolo[4,5-b]pyridin-3-yl ester

35 The title compound was prepared from [1,2,3]Triazolo[4,5-b]pyridin-3-ol and N-methyl-N-phenylcarbonyl chloride applying the general procedure 8. The crude product was purified

by flash chromatography (Quad flash 12, EtOAc-heptane) (99%, oil).

$^1\text{H}$  NMR (300MHz;  $\text{CDCl}_3$ ):  $\delta$  3.50 (bs, 3H), 7.30-7.60 (m, 6H), 8.40 (d, 1H), 8.75 (d, 1H);

HPLC-MS :  $m/z$  = 270.0 (M+1);  $R_t$  = 3.18 min.

5 **Example 310** (General procedure 8)Methyl-phenyl-carbamic acid 3-(2-nitro-phenyl)-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-3-(2-nitrophenyl)pyrazole and N-methyl-N-phenylcarbamoil chloride applying the general procedure 8. The crude product was purified

10 by flash chromatography (Quad flash 12, EtOAc-heptane) (94%, oil).

$^1\text{H}$  NMR (300MHz;  $\text{CDCl}_3$ ):  $\delta$  3.45 (bs, 3H), 6.44 (bs, 1H), 7.30-7.50 (m, 7H), 7.58 (dt, 1H), 7.72-7.78 (m, 2H); HPLC-MS :  $m/z$  = 339.1 (M+1);  $R_t$  = 4.15 min.

15 **Example 311** (General procedure 8)Methyl-phenyl-carbamic acid 3-(4-nitro-phenyl)-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-3-(4-nitrophenyl)pyrazole and N-methyl-N-phenylcarbamoil chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (99%, yellow crystals).

20  $^1\text{H}$  NMR (300MHz;  $\text{CDCl}_3$ ):  $\delta$  3.47 (bs, 3H), 6.70 (bd, 1H), 7.32-7.50 (m, 6H), 7.94 (d, 2H), 8.26 (d, 2H); HPLC-MS :  $m/z$  = 339.1 (M+1);  $R_t$  = 4.41 min.

**Example 312** (General procedure 8)Methyl-phenyl-carbamic acid 3-pyridin-2-yl-pyrazol-1-yl ester

25

The title compound was prepared from 1-hydroxy-3-(2-pyridyl)pyrazole and N-methyl-N-phenylcarbamoil chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (90%, oil).

30  $^1\text{H}$  NMR (300MHz;  $\text{CDCl}_3$ ):  $\delta$  3.48 (bs, 3H), 6.95 (d, 1H), 7.20 (dd, 1H), 7.30-7.48 (m, 6H), 7.70 (dt, 1H), 7.93 (d, 1H), 8.61 (d, 1H); HPLC-MS :  $m/z$  = 295.1 (M+1);  $R_t$  = 2.75 min.

**Example 313** (General procedure 8)Methyl-phenyl-carbamic acid 3-thiophen-2-yl-pyrazol-1-yl ester

35 The title compound was prepared from 1-hydroxy-3-(2-thienyl)pyrazole and N-methyl-N-

phenylcarbamoyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (66%, oil).

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  3.46 (bs, 3H), 6.48 (bd, 1H), 7.03 (dd, 1H), 7.25 (dd, 1H), 7.30-7.48 (m, 7H); HPLC-MS :  $m/z$  = 300.1 (M+1);  $R_t$  = 4.16 min.

5

**Example 314** (General procedure 8)Methyl-phenyl-carbamic acid 3-(2-fluoro-phenyl)-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-3-(2-fluorophenyl)pyrazole and N-methyl-N-phenylcarbamoyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (97%, oil).

10

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  3.48 (bs, 3H), 6.75 (bt, 1H), 7.07-7.47 (m, 9H), 7.97 (dt, 1H); HPLC-MS :  $m/z$  = 312.1 (M+1);  $R_t$  = 4.45 min.

15 **Example 315** (General procedure 8)Methyl-phenyl-carbamic acid 3-bromo-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-3-bromopyrazole and N-methyl-N-phenylcarbamoyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (63%, oil).

20 <sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  3.43 (bs, 3H), 6.31 (d, 1H), 7.26-7.48 (m, 6H).; HPLC-MS :  $m/z$  = 298.0 (M+1);  $R_t$  = 3.97 min.

**Example 316** (General procedure 8)Methyl-phenyl-carbamic acid 5-iodo-pyrazol-1-yl ester

25 The title compound was prepared from 1-hydroxy-5-iodopyrazole and N-methyl-N-phenylcarbamoyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (64%, oil).

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  3.48 (bs, 3H), 6.42 (d, 1H), 7.28-7.47 (m, 6H).; HPLC-MS :  $m/z$  = 343.9 (M+1);  $R_t$  = 3.81 min.

30

**Example 317** (General procedure 8)Methyl-phenyl-carbamic acid 2-chloro-imidazol-1-yl ester

35 The title compound was prepared from 1-hydroxy-2-chloroimidazole, hydrochloride and N-methyl-N-phenylcarbamoyl chloride applying the general procedure 8. The crude product

was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (77%, oil).

$^1\text{H}$  NMR (300MHz;  $\text{CDCl}_3$ ):  $\delta$  3.45 (bs, 3H), 6.90 (bs, 1H), 7.07 (bs, 1H), 7.35-7.40 (m, 3H), 7.46 (bt, 2H); HPLC-MS :  $m/z$  = 251.9 ( $\text{M}+1$ );  $R_t$  = 3.29 min.

5 **Example 318** (General procedure 8)Methyl-phenyl-carbamic acid 4-(4-methoxy-phenyl)-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-4-(4-methoxyphenyl)pyrazole and N-methyl-N-phenylcarbamoil chloride applying the general procedure 8. The crude product

10 was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (6%, oil).

$^1\text{H}$  NMR (300MHz;  $\text{CDCl}_3$ ):  $\delta$  3.45 (bs, 3H), 3.82 (s, 3H), 6.90 (d, 2H), 7.30-7.48 (m, 7H), 7.54 (bs, 2H); HPLC-MS :  $m/z$  = 346.1 ( $\text{M}+23$ );  $R_t$  = 4.16 min.

15 **Example 319** (General procedure 8)Methyl-phenyl-carbamic acid 5-benzoyl-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-5-benzoylpyrazole and N-methyl-N-phenylcarbamoil chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (30%, crystals).

20  $^1\text{H}$  NMR (300MHz;  $\text{CDCl}_3$ ):  $\delta$  3.48 (bs, 3H), 6.69 (bs, 1H), 7.27-7.52 (m, 8H), 7.63 (t, 1H), 7.79 (d, 2H); HPLC-MS :  $m/z$  = 344.0 ( $\text{M}+23$ );  $R_t$  = 4.41 min.

25 **Example 320** (General procedure 8)Methyl-phenyl-carbamic acid 5-(4-methoxy-phenyl)-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-5-(4-methoxyphenyl)pyrazole and N-methyl-N-phenylcarbamoil chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (38%, yellow crystals).

30  $^1\text{H}$  NMR (300MHz;  $\text{CDCl}_3$ ):  $\delta$  3.33 (bs, 3H), 3.86 (s, 3H), 6.34 (d, 1H), 6.95 (d, 2H), 7.25-7.45 (m, 8H); HPLC-MS :  $m/z$  = 324.1 ( $\text{M}+1$ );  $R_t$  = 4.27 min.

**Example 321** (General procedure 8)Methyl-phenyl-carbamic acid 5-(4-dimethylamino-phenyl)-pyrazol-1-yl ester



The title compound was prepared from 1-hydroxy-5-(4-dimethylaminophenyl)-pyrazole and N-methyl-N-phenylcarbamoyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (27%, crystals).

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  3.02 (s, 6H), 3.35 (bs, 3H), 6.30 (d, 1H), 6.72 (d, 2H), 7.30-7.46 (m, 8H); HPLC-MS :  $m/z$  = 337.1 (M+1);  $R_t$  = 4.11 min.

**Example 322** (General procedure 8)Methyl-phenyl-carbamic acid 4,5-diiodo-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-4,5-diiodopyrazole and N-methyl-N-phenylcarbamoyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (76%, crystals).

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  3.45 (bs, 3H), 7.30-7.50 (m, 6H).; HPLC-MS :  $m/z$  = 369.9 (M+1);  $R_t$  = 4.56 min.

**Example 323** (General procedure 8)Methyl-phenyl-carbamic acid 5-thiophen-2-yl-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-5-(2-thienyl)pyrazole and N-methyl-N-phenylcarbamoyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (51%, crystals).

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  3.44 (bs, 3H), 6.45 (bs, 1H), 7.09 (dd, 1H), 7.26 (bs, 1H), 7.28-7.49 (m, 7H); HPLC-MS :  $m/z$  = 300.1 (M+1);  $R_t$  = 4.18 min.

**Example 324** (General procedure 8)Methyl-phenyl-carbamic acid 2-(4-methoxy-phenyl)-imidazol-1-yl ester

The title compound was prepared from 1-hydroxy-2-(4-methoxyphenyl)imidazole, hydrochloride and N-methyl-N-phenylcarbamoyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (89%, crystals).

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  3.33 (bs, 3H), 3.86 (s, 3H), 6.92 (d, 2H), 7.04 (d, 1H), 7.10 (bs, 1H), 7.28 (d, 2H), 7.34-7.50 (m, 3H), 7.60 (bd, 2H); HPLC-MS :  $m/z$  = 324.1 (M+1);  $R_t$  = 2.87 min.

**Example 325** (General procedure 8) Methyl-phenyl-carbamic acid 2-methylsulfanyl-imidazol-1-yl ester

The title compound was prepared from 1-hydroxy-2-methylsulfanyl-imidazole hydrochloride and N-methyl-N-phenylcarbamoyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (97%, oil).

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  2.56 (s, 3H), 3.44 (bs, 3H), 7.00 (bs, 1H), 7.08 (bs, 1H), 7.32-7.49 (m, 5H); HPLC-MS :  $m/z$  = 264.1 (M+1); R<sub>t</sub> = 2.99 min.

**Example 326** (General procedure 8) Methyl-phenyl-carbamic acid 3,5-bis-(4-methoxyphenyl)-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-3,5-bis-(4-methoxyphenyl)pyrazole and N-methyl-N-phenylcarbamoyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (29%, beige crystals).

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  3.35 (bs, 3H), 3.84 (s, 3H), 3.88 (s, 3H), 6.57 (s, 1H), 6.92 (d, 2H), 6.97 (d, 2H), 7.25-7.48 (m, 7H), 7.74 (d, 2H); HPLC-MS :  $m/z$  = 881.2 (2M+23); R<sub>t</sub> = 5.26 min.

**Example 327** (General procedure 8) Methyl-phenyl-carbamic acid 4-(4-fluoro-phenyl)-5-(4-methoxy-phenyl)-3-(4-methylphenyl)-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-4-(4-fluorophenyl)-5-(4-methoxyphenyl)-3-(4-methylphenyl)pyrazole and N-methyl-N-phenylcarbamoyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (11%, crystals).

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  2.32 (s, 3H), 3.32 (bs, 3H), 3.83 (s, 3H), 6.87 (d, 2H), 6.93 (d, 2H), 7.12-7.48 (m, 13H); HPLC-MS :  $m/z$  = 530.2 (M+23); R<sub>t</sub> = 6.04 min.

**Example 328** (General procedure 8) Methyl-phenyl-carbamic acid 4-benzyl-5-(4-methoxyphenyl)-3-(methylphenyl)-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-4-benzyl-5-(4-methoxyphenyl)-3-(4-methylphenyl)pyrazole and N-methyl-N-phenylcarbamoyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-

heptane) (14%, oil).

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  2.31 (s, 3H), 3.31 (bs, 3H), 3.83 (s, 3H), 3.95 (s, 2H), 6.89 (d, 2H), 7.08-7.39 (m, 13H), 7.43 (d, 2H); HPLC-MS :  $m/z$  = 504.2 (M+1);  $R_t$  = 6.11 min.

5 **Example 329** (General procedure 8)Methyl-phenyl-carbamic acid 4-acetyl-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-4-acetylpyrazole and N-methyl-N-phenylcarbonyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (89%, oil).

10 <sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  2.44 (s, 3H), 3.44 (bs, 3H), 7.32-7.48 (m, 5H), 7.78 (bs, 1H), 7.85 (bs, 1H).

**Example 330** (General procedure 8)Methyl-phenyl-carbamic acid 2-(4-nitro-phenyl)-imidazol-1-yl ester

15

The title compound was prepared from 1-hydroxy-2-(4-nitrophenyl)imidazole, hydrochloride and N-methyl-N-phenylcarbonyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (90%, yellow crystals).

20 <sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  3.38 (bs, 3H), 7.16 (s, 1H), 7.20 (s, 1H), 7.31 (d, 2H), 7.38-7.61 (m, 3H), 7.86 (bs, 2H), 8.25 (d, 2H).

**Example 331** (General procedure 8)Methyl-phenyl-carbamic acid 2-chloro-5-(4-methylphenyl)-imidazol-1-yl ester

25

The title compound was prepared from 1-hydroxy-2-chloro-5-(4-methylphenyl)imidazole, hydrochloride and N-methyl-N-phenylcarbonyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (80%, oil).

30 <sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  2.40 (s, 3H), 3.33 (bs, 3H), 7.00 (s, 1H), 7.19-7.29 (m, 6H), 7.35-7.50 (m, 3H).

**Example 332** (General procedure 8)Methyl-phenyl-carbamic acid 4-formyl-pyrazol-1-yl ester

35 The title compound was prepared from 1-hydroxy-4-formylpyrazole and N-methyl-N-

phenylcarbamoyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (73%, oil).

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>): δ 3.45 (bs, 3H), 7.29-7.50 (m, 5H), 7.84 (bs, 1H), 7.90 (bs, 1H), 9.83 (s, 1H).

5

**Example 333** (General procedure 8) Methyl-phenyl-carbamic acid 4-hydroxymethyl-pyrazol-1-yl ester

10 The title compound was prepared from 1-hydroxy-4-hydroxymethylpyrazole and N-methyl-N-phenylcarbamoyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (62%, oil).

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>): δ 2.33 (bs, 1H), 3.40 (bs, 3H), 4.50 (s, 2H), 7.28-7.46 (m, 7H).

15 **Example 334** (General procedure 8) Methyl-phenyl-carbamic acid 4-phenylethynyl-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-4-phenylethynylpyrazole and N-methyl-N-phenylcarbamoyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (40%, yellow crystals).

20 <sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>): δ 3.42 (bs, 3H), 7.30-7.58 (m, 12H).

**Example 335** (General procedure 8) Methyl-phenyl-carbamic acid 2-bromo-imidazol-1-yl ester

25 The title compound was prepared from 1-hydroxy-2-bromoimidazole, hydrochloride and N-methyl-N-phenylcarbamoyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (63%, oil).

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>): δ 3.45 (bs, 3H), 6.98 (bd, 1H), 7.11 (bs, 1H), 7.33-7.50 (m, 5H); HPLC-MS : m/z = 296.0 (M+1); R<sub>t</sub> = 2.90 min.

30

**Example 336** (General procedure 8) Methyl-phenyl-carbamic acid 2-phenylsulfanyl-imidazol-1-yl ester

35 The title compound was prepared from 1-hydroxy-2-phenylsulfanylimidazole hydrochloride and N-methyl-N-phenylcarbamoyl chloride applying the general procedure 8. The crude

product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (61%, oil).

$^1\text{H}$  NMR (300MHz;  $\text{CDCl}_3$ ):  $\delta$  3.35 (s, 3H), 7.12 (bd, 1H), 7.17-7.39 (m, 11H); HPLC-MS :  $m/z$  = 326.0 (M+1);  $R_t$  = 3.65 min.

5 **Example 337** (General procedure 8)Morpholine-4-carboxylic acid imidazol-1-yl ester

The title compound was prepared from 1-hydroxyimidazole and 4-morpholine carbonyl chloride applying the general procedure 8. The crude product was purified by preparative HPLC (water-acetonitrile-0.1% TFA) (36%, crystals).

10  $^1\text{H}$  NMR (300MHz;  $\text{CDCl}_3$ ):  $\delta$  3.57 (bs, 2H), 3.66 (bs, 2H), 3.78 (t, 4H), 7.12 (bs, 1H), 7.15 (bt, 1H), 7.90 (s, 1H); HPLC-MS :  $m/z$  = 198.1 (M+1);  $R_t$  = 0.36 min.

**Example 338** (General procedure 8)Morpholine-4-carboxylic acid 2-bromo-imidazol-1-yl ester

15

The title compound was prepared from 1-hydroxy-2-bromoimidazole, hydrochloride and 4-morpholine carbonyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc) (98%, crystals).

$^1\text{H}$  NMR (300MHz;  $\text{CDCl}_3$ ):  $\delta$  3.60 (bs, 2H), 3.71 (bs, 2H), 3.80 (t, 4H), 7.02 (d, 1H), 7.18 (d, 20 1H); HPLC-MS :  $m/z$  = 276.0 (M+1);  $R_t$  = 1.73 min.

**Example 339** (General procedure 8)Morpholine-4-carboxylic acid 2-chloro-imidazol-1-yl ester

25 The title compound was prepared from 1-hydroxy-2-chloroimidazole, hydrochloride and 4-morpholine carbonyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc) (54%, oil).

$^1\text{H}$  NMR (300MHz;  $\text{CDCl}_3$ ):  $\delta$  3.58 (bs, 2H), 3.68 (bs, 2H), 3.69 (t, 4H), 6.94 (d, 1H), 7.10 (d, 1H); HPLC-MS :  $m/z$  = 232.0 (M+1);  $R_t$  = 1.69 min.

30

**Example 340** (General procedure 8)Morpholine-4-carboxylic acid 2-phenylsulfanyl-imidazol-1-yl ester

35 The title compound was prepared from 1-hydroxy-2-phenylsulfanylimidazole, hydrochloride and 4-morpholine carbonyl chloride applying the general procedure 8. The crude product

was purified by flash chromatography (Quad flash 12, EtOAc) (98%, oil).

$^1\text{H}$  NMR (300MHz;  $\text{CDCl}_3$ ):  $\delta$  3.46 (bs, 4H), 3.66 (bs, 4H), 7.15 (d, 1H), 7.18-7.31 (m, 6H);

HPLC-MS :  $m/z$  = 306.1 (M+1);  $R_t$  = 2.75 min.

5 **Example 341** (General procedure 8)Morpholine-4-carboxylic acid 2-(4-methoxy-phenyl)-imidazol-1-yl ester

The title compound was prepared from 1-hydroxy-2-(4-methoxyphenyl)imidazole, hydrochloride and 4-morpholine carbonyl chloride applying the general procedure 8. The crude product  
10 was purified by flash chromatography (Quad flash 12, EtOAc) (49%, crystals).

$^1\text{H}$  NMR (300MHz;  $\text{CDCl}_3$ ):  $\delta$  3.51 (bs, 2H), 3.62-3.76 (m, 6H), 3.86 (s, 3H), 6.96 (d, 2H), 7.08 (d, 1H), 7.11 (d, 1H), 7.70 (d, 2H); HPLC-MS :  $m/z$  = 304.1 (M+1);  $R_t$  = 1.81 min.

15 **Example 342** (General procedure 8)Morpholine-4-carboxylic acid 4-bromo-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-4-bromopyrazole and 4-morpholine carbonyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (85%, crystals).

20  $^1\text{H}$  NMR (300MHz;  $\text{CDCl}_3$ ):  $\delta$  3.57 (bs, 2H), 3.68 (bs, 2H), 3.79 (t, 4H), 7.35 (d, 1H), 7.43 (d, 1H); HPLC-MS :  $m/z$  = 298.0 (M+23);  $R_t$  = 2.46 min.

**Example 343** (General procedure 8)Morpholine-4-carboxylic acid 4-iodo-pyrazol-1-yl ester

25 The title compound was prepared from 1-hydroxy-4-iodopyrazole and 4-morpholine carbonyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (99%, crystals).

$^1\text{H}$  NMR (300MHz;  $\text{CDCl}_3$ ):  $\delta$  3.56 (bs, 2H), 3.66 (bs, 2H), 3.77 (t, 4H), 7.41 (d, 1H), 7.44 (d, 1H); HPLC-MS :  $m/z$  = 324.0 (M+1);  $R_t$  = 2.65 min.

30 **Example 344** (General procedure 8)Morpholine-4-carboxylic acid 3,4,5-tribromo-pyrazol-1-yl ester

35 The title compound was prepared from 1-hydroxy-3,4,5-tribromopyrazole and 4-morpholine carbonyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (90%, crystals).

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  3.59 (bs, 2H), 3.69 (bs, 2H), 3.79 (t, 4H); HPLC-MS :  $m/z$  = 455.6 (M+23); R<sub>t</sub> = 3.91 min.

**Example 345** (General procedure 8)

5 **Morpholine-4-carboxylic acid 3-(4-methoxy-phenyl)-pyrazol-1-yl ester**

The title compound was prepared from 1-hydroxy-3-(4-methoxyphenyl)pyrazole and 4-morpholine carbonyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (62%, crystals).

10 <sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  3.58 (bs, 2H), 3.71 (bs, 2H), 3.79 (t, 4H), 3.84 (s, 3H), 6.53 (d, 1H), 6.92 (d, 2H), 7.40 (d, 1H), 7.71 (d, 2H); HPLC-MS :  $m/z$  = 326.0 (M+23); R<sub>t</sub> = 3.21 min.

**Example 346** (General procedure 8) **Morpholine-4-carboxylic acid 3-thiophen-2-yl-pyrazol-1-yl ester**

15

The title compound was prepared from 1-hydroxy-3-(2-thienyl)pyrazole and 4-morpholine carbonyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (75%, crystals).

20 <sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  3.57 (bs, 2H), 3.69 (bs, 2H), 3.79 (t, 4H), 6.51 (d, 1H), 7.04 (dd, 1H), 7.26 (dd, 1H), 7.34 (dd, 1H), 7.40 (d, 1H); HPLC-MS :  $m/z$  = 280.0 (M+1); R<sub>t</sub> = 3.12 min.

**Example 347** (General procedure 8) **Morpholine-4-carboxylic acid pyrazol-1-yl ester**

25 The title compound was prepared from 1-hydroxypyrazole and 4-morpholine carbonyl chloride applying the general procedure 8. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (94%, crystals).

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  3.57 (bs, 2H), 3.69 (bs, 2H), 3.79 (t, 4H), 6.32 (t, 1H), 7.38 (dd, 1H), 7.41 (dd, 1H); HPLC-MS :  $m/z$  = 198.0 (M+1); R<sub>t</sub> = 1.18 min.

30 **Example 348** (General procedure 16) **4-Methyl-piperazine-1-carboxylic acid pyrazol-1-yl ester**

35 The title compound was prepared from 1-hydroxypyrazole and N-methylpiperazine applying the general procedure 16. The crude product was purified by preparative HPLC (water-acetonitrile-0.1% TFA) (17%, salt with TFA).

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>): δ 2.36 (s, 3H), 2.50 (bt, 4H), 3.59 (bs, 2H), 3.71 (bs, 2H), 6.31 (t, 1H), 7.38 (dd, 1H), 7.40 (dd, 1H); HPLC-MS : *m/z* = 211.0 (M+1); R<sub>t</sub> = 0.40 min.

**Example 349** (General procedure 16) 4-Cyclopentyl-piperazine-1-carboxylic acid pyrazol-1-yl ester

The title compound was prepared from 1-hydroxypyrazole and N-cyclopentylpiperazine applying the general procedure 16. The crude product was purified by preparative HPLC (water-acetonitrile-0.1% TFA) (34%, salt with TFA).

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>): δ 1.45-2.01 (m, 8H), 2.70 (bs, 4H), 2.92 (bs, 1H), 3.55 (bt, 1H), 3.63 (bs, 2H), 3.77 (bs, 2H), 6.31 (t, 1H), 7.38 (dd, 1H), 7.41 (dd, 1H); HPLC-MS : *m/z* = 265.1 (M+1); R<sub>t</sub> = 0.54 min.

**Example 350** (General procedure 16) 4-Phenyl-piperazine-1-carboxylic acid pyrazol-1-yl ester

The title compound was prepared from 1-hydroxypyrazole and N-phenylpiperazine applying the general procedure 16. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (48%, crystals).

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>): δ 3.25 (bt, 4H), 3.72 (bs, 2H), 3.85 (bs, 2H), 6.33 (t, 1H), 6.92-6.98 (m, 3H), 7.27-7.33 (m, 2H), 7.38 (dd, 1H), 7.41 (dd, 1H); HPLC-MS : *m/z* = 273.1 (M+1); R<sub>t</sub> = 3.06 min.

**Example 351** (General procedure 16) 4-Pyridin-2-yl-piperazine-1-carboxylic acid pyrazol-1-yl ester

The title compound was prepared from 1-hydroxypyrazole and 1-(2-pyridyl)piperazine applying the general procedure 16. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (59%, crystals).

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>): δ 3.62-3.85 (m, 8H), 6.32 (t, 1H), 6.66-6.72 (m, 2H), 7.39 (dd, 1H), 7.42 (dd, 1H), 7.53 (dt, 1H), 8.21 (d, 1H); HPLC-MS : *m/z* = 274.1 (M+1); R<sub>t</sub> = 0.63 min.

**Example 352** (General procedure 16) 4-Pyrimidin-2-yl-piperazine-1-carboxylic acid pyrazol-1-yl ester



The title compound was prepared from 1-hydroxypyrazole and 1-(2-pyrimidyl)piperazine applying the general procedure 16. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (57%, crystals).

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  3.65 (bs, 2H), 3.78 (bs, 2H), 3.95 (bs, 4H), 6.32 (t, 1H), 6.58 (t, 2H), 7.38 (dd, 1H), 7.42 (dd, 1H), 8.35 (d, 1H); HPLC-MS :  $m/z$  = 275.2 (M+1);  $R_t$  = 2.14 min.

**Example 353** (General procedure 16)4-Benzo[1,3]dioxol-5-yl-piperazine-1-carboxylic acid pyrazol-1-yl ester

The title compound was prepared from 1-hydroxypyrazole and 1-Benzo[1,3]dioxol-5-ylpiperazine applying the general procedure 16. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (92%, crystals).

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  3.11 (bt, 4H), 3.71 (bs, 2H), 3.83 (bs, 2H), 5.93 (s, 2H), 6.32 (t, 1H), 6.39 (dd, 1H), 6.57 (d, 1H), 6.74 (d, 1H), 7.37 (dd, 1H), 7.41 (dd, 1H); HPLC-MS :  $m/z$  = 317.2 (M+1);  $R_t$  = 2.96 min.

**Example 354** (General procedure 16)4-Benzyl-piperazine-1-carboxylic acid 4-iodo-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-4-iodopyrazole and 1-benzylpiperazine applying the general procedure 16. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (32%, oil).

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  2.53 (bs, 4H), 3.57 (bs, 4H), 3.67 (bs, 2H), 7.28-7.38 (m, 5H), 7.40 (d, 1H), 7.43 (d, 1H); HPLC-MS :  $m/z$  = 413.0 (M+1);  $R_t$  = 1.75 min.

**Example 355** (General procedure 16)4-Cyclopentyl-piperazine-1-carboxylic acid 4-iodo-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-4-iodopyrazole and N-

cyclopentylpiperazine applying the general procedure 16. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane-3% Et<sub>3</sub>N) (61%, crystals).

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  1.33-1.94 (m, 8H), 2.46-2.61 (m, 5H), 3.57 (bt, 2H), 3.67 (bt, 2H), 3.63 (bs, 2H), 3.77 (bs, 2H), 7.40 (d, 1H), 7.44 (d, 1H); HPLC-MS :  $m/z$  = 391.1 (M+1);  $R_t$  = 1.31 min.

**Example 356** (General procedure 16)4-(4-Fluoro-benzyl)-piperazine-1-carboxylic acid 4-iodo-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-4-iodopyrazole and 1-(4-

5 fluorobenzyl)piperazine applying the general procedure 16. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (48%, crystals).

$^1\text{H}$  NMR (300MHz;  $\text{CDCl}_3$ ):  $\delta$  2.50 (t, 4H), 3.51 (s, 2H), 3.57 (bt, 2H), 3.66 (bt, 2H), 7.02 (t, 2H), 7.29 (dd, 2H), 7.40 (d, 1H), 7.43 (d, 1H); HPLC-MS :  $m/z$  = 431.0 (M+1);  $R_t$  = 1.79 min.

10 **Example 357** (General procedure 16)4-Phenyl-piperazine-1-carboxylic acid 4-iodo-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-4-iodopyrazole and N-phenylpiperazine applying the general procedure 16. The crude product was purified by flash chromatography  
15 (Quad flash 12, EtOAc-heptane) (52%, crystals).

$^1\text{H}$  NMR (300MHz;  $\text{CDCl}_3$ ):  $\delta$  3.25 (t, 4H), 3.72 (bs, 2H), 3.81 (bs, 2H), 6.90-6.97 (m, 3H), 7.30 (t, 2H), 7.41 (d, 1H), 7.47 (d, 1H); HPLC-MS :  $m/z$  = 399.1 (M+1);  $R_t$  = 3.91 min.

20 **Example 358** (General procedure 16)4-Pyridin-2-yl-piperazine-1-carboxylic acid 4-iodo-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-4-iodopyrazole and 1-(2-pyridyl)piperazine applying the general procedure 16. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (45%, crystals).

25  $^1\text{H}$  NMR (300MHz;  $\text{CDCl}_3$ ):  $\delta$  3.62-3.82 (m, 8H), 6.66-6.72 (m, 2H), 7.42 (d, 1H), 7.47 (d, 1H), 7.54 (dt, 1H), 8.22 (d, 1H); HPLC-MS :  $m/z$  = 400.0 (M+1);  $R_t$  = 1.47 min.

30 **Example 359** (General procedure 16)4-Pyrimidin-2-yl-piperazine-1-carboxylic acid 4-iodo-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-4-iodopyrazole and 1-(2-pyrimidyl)piperazine applying the general procedure 16. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (10%, crystals).

35  $^1\text{H}$  NMR (300MHz;  $\text{CDCl}_3$ ):  $\delta$  3.62 (bs, 2H), 3.72 (bs, 2H), 3.95 (bs, 4H), 6.58 (t, 2H), 7.41 (d, 1H), 7.46 (d, 1H), 8.36 (d, 1H); HPLC-MS :  $m/z$  = 401.0 (M+1);  $R_t$  = 3.09 min.

**Example 360** (General procedure 16) 4-Benzo[1,3]dioxol-5-yl-piperazine-1-carboxylic acid 4-iodo-pyrazol-1-yl ester

- 5 The title compound was prepared from 1-hydroxy-4-iodopyrazole and 1-Benzo[1,3]dioxol-5-ylpiperazine applying the general procedure 16. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (59%, crystals).  
1<sup>H</sup> NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  3.11 (t, 4H), 3.69 (bs, 2H), 3.80 (bs, 2H), 5.92 (s, 2H), 6.38 (dd, 1H), 6.56 (d, 1H), 6.73 (d, 1H), 7.41 (d, 1H), 7.45 (d, 1H); HPLC-MS :  $m/z$  = 443.0 (M+1); R<sub>t</sub>  
10 = 3.79 min.

**Example 361**

4-(1-Ethylpropyl)piperazine-1-carboxylic acid 3-trifluoromethylphenyl ester hydrochloride salt

- 15 To a stirred mixture of 1-(1-ethylpropyl)piperazine (175  $\mu$ l, 1.0 mmol) and dry DCM (10 ml) was added 3-trifluoromethylphenyl chloroformate (250 mg, 1.1 mmol). The mixture was stirred overnight at room temperature and then diluted with DCM (50 ml). The reaction mixture was washed with 1 N NaOH (3 x 25 ml) and water (2 x 25 ml). The organic solution was concentrated and the residue was dissolved in a 0.5 N HCl solution (15 ml) and a small portion of acetonitrile. The  
20 acidic solution was concentrated and stirred with ethyl acetate (15 ml). The solid was isolated and dried to give 330 mg (86 %) of the title compound as a solid.  
M.p. 260-261°C.  
1<sup>H</sup> NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  0.98 (t, 6H), 1.63 (hept, 2H), 1.86-1.98 (m, 2H), 3.03-3.12 (m, 1H), 3.12-3.31 (m, 2H), 3.41-3.49 (m, 2H), 3.52-3.85 (m, 2H), 4.05-4.35 (m, 2H), 7.47-7.70 (m,  
25 4H), 11.0 (brs, 1H).

**Example 362**

4-(1-Ethylpropyl)piperazine-1-carboxylic acid naphthalen-1-yl ester hydrochloride salt

- 30 To a stirred mixture of 1-(1-ethylpropyl)piperazine (175  $\mu$ l, 1.0 mmol) and dry DCM (10 ml) was added 1-naphthalenyl chloroformate (225 mg, 1.1 mmol). The mixture was stirred overnight at room temperature and then diluted with DCM (50 ml). The reaction mixture was washed with 1 N NaOH (3 x 25 ml) and water (2 x 25 ml). The organic solution was concentrated and the residue was dissolved in a 0.5 N HCl solution (15 ml) and a small portion of acetonitrile. The acidic  
35 solution was concentrated and stirred with ethyl acetate (15 ml). The solid was isolated and

dried to give 310 mg (85 %) of the title compound as a solid.

M.p. 288-290°C.

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 1.00 (t, 6H), 1.63 (hept, 2H), 1.86-2.02 (m, 2H), 3.07-3.18 (m, 1H), 3.18-3.42 (m, 2H), 3.42-3.55 (m, 2H), 3.55-3.73 (m, 1H), 3.78-3.95 (m, 1H), 4.05-4.25 (m, 1H), 4.35-4.55 (m, 1H), 7.35 (d, 1H), 7.53 (t, 1H), 7.56-7.7.61 (m, 2H), 7.85 (d, 1H), 7.90-8.05 (m, 2H), 10.75 (brs, 1H).

### Example 363

4-(1-Ethylpropyl)piperazine-1-carboxylic acid 4-fluorophenyl ester hydrochloride salt

To a stirred mixture of 1-(1-ethylpropyl)piperazine (350 µl, 2.0 mmol) and dry DCM (15 ml) was added 4-fluorophenyl chloroformate (350 mg, 2.0 mmol). The mixture was stirred overnight at room temperature and then diluted with DCM (50 ml). The reaction mixture was washed with 1 N NaOH (3 x 25 ml) and water (2 x 25 ml). The organic solution was concentrated and the residue was re-evaporated twice with acetonitrile to give 590 mg of the free base. The hydrochloride salt was prepared from 465 mg free base by addition of a 0.5 N HCl solution (15 ml) and a small portion of acetonitrile. The acidic solution was concentrated and stirred with ethyl acetate (15 ml). The solid was isolated and dried to give 470 mg (90 %) of the title compound as a solid.

M.p. 275-277°C.

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 0.98 (t, 6H), 1.64 (hept, 2H), 1.85-1.95 (m, 2H), 3.02-3.11 (m, 1H), 3.11-3.28 (m, 2H), 3.38-3.46 (m, 2H), 3.50-3.80 (m, 2H), 4.00-4.30 (m, 2H), 7.18-7.26 (m, 4H), 10.85 (brs, 1H).

### Example 364

4-(1-Ethylpropyl)piperazine-1-carboxylic acid 2-nitrophenyl ester hydrochloride salt

To a stirred mixture of 1-(1-ethylpropyl)piperazine (175 µl, 1.0 mmol) and dry DCM (10 ml) was added 2-nitrophenyl chloroformate (201 mg, 1.0 mmol). The mixture was stirred overnight at room temperature and then diluted with DCM (50 ml). The reaction mixture was washed with 1 N NaOH (3 x 25 ml) and water (2 x 25 ml). The organic solution was concentrated and the residue was dissolved in a 0.5 N HCl solution (15 ml). The acidic solution was concentrated and

stirred with ethyl acetate (15 ml). The solid was isolated and dried to give 310 mg (86 %) of the title compound as a solid.

M.p. 251-253°C.

5 <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 0.96 (t, 6H), 1.65 (hept, 2H), 1.83-1.95 (m, 2H), 3.06-3.25 (m, 3H), 3.42-3.53 (m, 2H), 3.53-3.83 (m, 2H), 4.02-4.13 (m, 1H), 4.20-4.34 (m, 1H), 7.50-7.55 (m, 2H), 7.83 (t, 1H), 8.13 (d, 1H), 10.9 (brs, 1H).

10 **Example 365** 4-(1-Ethylpropyl)piperazine-1-carboxylic acid 4-methoxycarbonylphenyl ester hydrochloride salt

To a stirred mixture of 1-(1-ethylpropyl)piperazine (350 μl, 2.0 mmol) and dry DCM (15 ml) was  
15 added 4-methoxycarbonylphenyl chloroformate (430 mg, 2.0 mmol). The mixture was stirred overnight at room temperature and then diluted with DCM (50 ml). The reaction mixture was washed with 1 N NaOH (3 x 25 ml) and water (2 x 25 ml). The organic solution was concentrated and re-evaporated twice with acetonitrile. The residue was dissolved in a 0.5 N HCl solution (15 ml) and a small portion of acetonitrile. The acidic solution was concentrated and stirred  
20 with ethyl acetate (15 ml). The solid was isolated and dried to give 670 mg (90 %) of the title compound as a solid.

M.p. 248°C decomp.

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 0.97 (t, 6H), 1.63 (hept, 2H), 1.85-1.95 (m, 2H), 3.02-3.11 (m,  
25 1H), 3.11-3.30 (m, 2H), 3.40-3.48 (m, 2H), 3.50-3.80 (m, 2H), 3.85 (s, 3H), 4.05-4.33 (m, 2H), 7.33 (d, 2H), 8.00 (d, 2H), 10.7 (brs, 1H).

### **Example 366**

Methyl-phenyl-carbamic acid 5-(3,3-dimethyl-butrylamino)-pyridin-2-yl ester

30

A solution of N-(6-hydroxy-pyridin-3-yl)-3,3-dimethyl-butryamide (0.42 g, 2.00 mmol), N-methyl-N-phenylcarbonyl chloride (0.37 g, 2.20 mmol) and 1,4-diazabicyclo[2,2,2]octane (0.25 g, 2.20 mmol) in tetrahydrofuran (20 mL) was stirred at room temperature for 2.5 hours. Water was added and the solution was extracted three times with dichloromethane. The  
35 combined organic layers were dried over sodium sulphate, filtered and evaporated in vacuo.

The residue was redissolved in ethyl acetate and the solution was filtered over a short pad of silicagel. Evaporation of the solvent and crystallisation of the solid from ethyl acetate:heptane yielded the title compound (0.54 g, 79% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 1.03 (s, 9H), 2.15 (s, 2H), 3.47 (br.s, 3H), 6.91 (br.s, 1H), 7.27 (m, 1H), 7.38 (m, 4H), 7.99 (br.s + dd, 2H), 8.13 (d, 1H); HPLC-MS (Method A): m/z = 342 (M+H)<sup>+</sup>; Rt = 3.67 min.

#### Example 367

Methyl-phenyl-carbamic acid 5-[(pyridine-2-carbonyl)-amino]-pyridin-2-yl ester

10

A solution of pyridine-2-carboxylic acid (6-hydroxy-pyridin-3-yl)-amide hydrochloride (0.50 g, 1.99 mmol), N-methyl-N-phenylcarbonyl chloride (0.44 g, 2.59 mmol) and 1,4-diazabicyclo[2,2,2]octane (0.54 g, 4.81 mmol) in dimethylformamide (15 mL) was stirred at room temperature for 1 hour. Water was added and the solids were isolated by suction, re-

15 dissolved in dichloromethane. The solution was dried over sodium sulphate, filtered and evaporated in vacuo. The residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane 50:50) yielding the title compound (0.38 g, 55% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 3.45 (br.s, 3H), 7.11 (br.s, 1H), 7.26 (m, 1H), 7.40 (d, 4H), 7.51 (m, 1H), 7.92 (dt, 1H), 8.28 (d, 1H), 8.45 (dd, 1H), 8.60 (m, 2H), 10.10 (s, 1H); HPLC-

20 MS (Method A): m/z = 349 (M+H)<sup>+</sup>; Rt = 3.31 min.

#### Example 368

Methyl-phenyl-carbamic acid 2-(4,4-dimethyl-2,6-dioxo-piperidin-1-yl)-pyrimidin-5-yl ester

25 A solution of 1-(5-hydroxy-pyrimidin-2-yl)-4,4-dimethyl-piperidine-2,6-dione (0.60 g, 2.55 mmol), N-methyl-N-phenylcarbonyl chloride (0.48 g, 2.81 mmol) and 1,4-diazabicyclo[2,2,2]octane (0.31 g, 2.81 mmol) in dichloromethane (25 mL) was stirred at room temperature for 15 minutes. The solvent was evaporated in vacuo and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane 50:50), yielding the title com-

30 pound as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 1.22 (s, 6H), 2.65 (s, 4H), 3.44 (br.s, 3H), 7.28-7.48 (m, 5H), 8.68 (br.s, 2H); HPLC-MS (Method A): m/z = 369 (M+H)<sup>+</sup>; Rt = 3.45 min.

#### Example 369

35 Methyl-phenyl-carbamic acid 5-bromo-pyrimidin-2-yl ester

A mixture of 4-bromo-2-hydroxypyrimidine (0.96 g, 5.49 mmol), N-methyl-N-phenylcarbamoyl chloride (1.02 g, 6.04 mmol) and 1,4-diazabicyclo[2,2,2]octane (0.68 g, 6.04 mmol) in dry tetrahydrofuran (15mL) was stirred at room temperature for 1 hour. Dichloromethane was added and the solution was extracted twice with water. The organic layer was dried over sodium sulphate, filtered and evaporated in vacuo yielding the title compound (1.70 g, 100% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 3.43 (br.s, 3H), 7.27 (m, 1H), 7.38 (m, 4H), 8.68 (br.s, 2H); HPLC-MS (Method A): m/z = 330 and 332 (M+H)<sup>+</sup>; Rt = 3.33 min.

#### Example 370

Methyl-phenyl-carbamic acid 5-[(6-chloro-pyridine-3-carbonyl)-amino]-pyridin-2-yl ester

A mixture of 4-chloro-N-(6-hydroxy-pyridin-3-yl)-nicotinamide (0.56 g, 2.25 mmol), N-methyl-N-phenylcarbamoyl chloride (0.51 g, 3.00 mmol) and 1,4-diazabicyclo[2,2,2]octane (0.67 g, 6.00 mmol) in dry tetrahydrofuran (15mL) was stirred at room temperature for 1 hour. Dichloromethane was added and the solution was extracted twice with water. The organic layer was dried over sodium sulphate, filtered and evaporated in vacuo. The residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane 70:30) followed by crystallised from ethyl acetate:heptane, yielding the title compound (44 mg, 5% yield) HPLC-MS (Method A): m/z = 383 (M+H)<sup>+</sup>; Rt = 3.40 min.

#### Example 371

Methyl-phenyl-carbamic acid 5-(2,2-dimethyl-propylcarbamoyl)-pyridin-2-yl ester

A solution of N-(2,2-dimethyl-propyl)-6-hydroxy-nicotinamide (0.50 g, 2.40 mmol), N-methyl-N-phenylcarbamoyl chloride (0.41 g, 2.40 mmol) and 1,4-diazabicyclo[2,2,2]octane (0.27 g, 2.40 mmol) in tetrahydrofuran (15 mL) was stirred at room temperature for 3 hours. The solvent was evaporated in vacuo and the residue was purified by flash column chromatography (first column: SiO<sub>2</sub>, dichloromethane:ethyl acetate 95:5, second column: SiO<sub>2</sub>, ethyl acetate), yielding the title compound (0.43 g, 52% yield).

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 0.97 (s, 9H), 3.26 (d, 2H), 3.44 (br.s, 3H), 6.26 (br.s, 1H), 7.08 (br.s, 1H), 7.29 (m, 1H), 7.39 (m, 4H), 8.13 (br.d, 1H), 8.70 (br.s, 1H); HPLC-MS (Method A): m/z = 383 (M+H)<sup>+</sup>; Rt = 3.40 min.

**Example 372**

[Methyl-phenyl-carbamic acid 6-(3,4-dichloro-phenoxy)-pyridazin-3-yl ester

A solution of 6-(3,4-dichloro-phenoxy)-pyridazin-3-ol (0.51 g, 2.00 mmol), N-methyl-N-phenylcarbonyl chloride (0.36g, 2.10 mmol) and 1,4-diazabicyclo[2,2,2]octane (0.24 g, 2.10 mmol) in tetrahydrofuran (15 mL) was stirred at room temperature for 2 hours. The solvent was evaporated in vacuo and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane 30:70), yielding the title compound (0.34 g, 44% yield).  
<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 3.43 (br.s, 3H), 7.10 (dd, 1H), 7.20-7.51 (m, 9H); HPLC-MS (Method A): m/z = 389 (M+H)<sup>+</sup>; Rt = 4.56 min.

**Example 373**

4-(tert-Butyl-dimethyl-silanyloxy)-piperidine-1-carboxylic acid 5-benzoylamino-pyridin-2-yl ester

A solution of N-(6-hydroxy-pyridin-3-yl)-benzamide (214 mg, 1.00 mmol), 3-[4-(tert-butyl-dimethyl-silanyloxy)-piperidine-1-carbonyl]-1-methyl-3H-imidazol-1-ium iodide (451 mg, 1.00 mmol) and 1,4-diazabicyclo[2,2,2]octane (112 mg, 1.00 mmol) in dimethylformamide (10 mL) was stirred for 18 hours at room temperature followed by heating for 3 days at 40 °C. The solvent was evaporated in vacuo and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane 40:60), yielding the title compound (364 mg, 77% yield).  
<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 0.08 (s, 6H), 0.91 (s, 9H), 1.59 (m, 2H), 1.78 (m, 2H), 3.50 (m, 1H), 3.62 (m, 2H), 3.76 (m, 1H), 4.00 (m, 1H), 6.87 (d, 1H), 7.41 (m, 2H), 7.50 (m, 1H), 7.90 (d, 2H), 8.01 (dd, 1H), 8.36 (d, 1H), 9.03 (s, 1H, NH); HPLC-MS (Method A): m/z = 456 (M+H)<sup>+</sup>; Rt = 5.23 min.

**Example 374**

4-Hydroxy-piperidine-1-carboxylic acid 5-benzoylamino-pyridin-2-yl ester

Hydrofluoric acid (min. 40% in water, 0.50 mL) was added to a stirred solution of 4-(tert-butyl-dimethyl-silanyloxy)-piperidine-1-carboxylic acid 5-benzoylamino-pyridin-2-yl ester (364 mg, 0.77 mmol) in acetonitrile. After stirring overnight at room temperature the solvent was evaporated in vacuo. The residue was redissolved in dichloromethane. After addition of triethylamine (1 mL) the solution was filtered over a short pad of silicagel and washed with ethyl acetate:acetone 50:50. Evaporation of the solvent yielded the title compound (180 mg,



68% yield) as a white solid.

<sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ = 1.60 (m, 2H), 1.91 (m, 2H), 3.25 (m, 2H), 4.02 (m, 1H), 4.41 (d, 1H), 7.07 (d, 1H), 7.44-7.61 (m, 3H), 7.99 (m, 2H), 8.35 (dd, 1H), 8.72 (d, 1H), 10.19 (s, 1H, NH); HPLC-MS (Method A): m/z = 342 (M+H)<sup>+</sup>; Rt = 2.37 min.

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### Example 375

4-Hydroxy-piperidine-1-carboxylic acid 5-trifluoromethyl-pyridin-2-yl ester

A solution of 2-hydroxy-5-trifluoromethylpyridine (0.32 g, 2.00 mmol), 4-(tert-butyl-dimethyl-silanyloxy)-piperidine-1-carboxylic acid 5-benzoylamino-pyridin-2-yl ester (0.90 g, 2.00 mmol) and triethylamine (0.20 g, 2.00 mmol) in acetonitrile (10 mL) was stirred at room temperature for three days. Hydrofluoric acid (min. 40% in water, 0.50 mL) was added and stirring was continued for 18 hours. The solvent was evaporated in vacuo and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane 75:25), followed by crystallisation from ethyl acetate:heptane, yielding the title compound (0.27 g, 47% yield) as a white solid. <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 1.64 (m, 3H, 2 x CH + OH), 1.96 (m, 2H), 3.33 (m, 1H), 3.45 (m, 1H), 4.00 (m, 3H), 7.27 (d, 1H), 8.00 (dd, 1H), 8.64 (d, 1H); HPLC-MS (Method A): m/z = 313 (M+Na)<sup>+</sup>; Rt = 2.45 min.

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### Example 376

4-Hydroxy-piperidine-1-carboxylic acid 5-(4-chloro-benzoylamino)-pyridin-2-yl ester

A solution of 4-chloro-N-(6-hydroxy-pyridin-3-yl)-benzamide (0.50 g, 2.00 mmol), 4-(tert-butyl-dimethyl-silanyloxy)-piperidine-1-carboxylic acid 5-benzoylamino-pyridin-2-yl ester (0.90 g, 2.00 mmol) and triethylamine (0.20 g, 2.00 mmol) in dimethylformamide (10 mL) was stirred overnight at room temperature. The solvent was evaporated in vacuo. The residue was dissolved in dichloromethane, filtered over a short pad of silicagel and washed with ethyl acetate:heptane 50:50. The solvent was evaporated in vacuo and the residue was redissolved in acetonitrile and hydrofluoric acid (min. 40% in water, 0.50 mL) was added. After stirring overnight at room temperature the solvent was evaporated in vacuo. Dichloromethane and triethylamine (1 mL) were added and the solution was extracted twice with water, dried over sodium sulphate, filtered and evaporated in vacuo. Crystallisation from ethyl acetate:heptane yielded the title compound (321 mg, 43% yield).

<sup>1</sup>H NMR (300MHz, DMSO-d<sub>6</sub>): δ = 1.50 (m, 2H), 1.80 (m, 2H), 3.16 (m, 1H), 3.31 (m, 1H), 3.75 (m, 2H), 3.88 (m, 1H), 4.81 (d, 1H), 7.18 (d, 1H), 7.62 (d, 2H), 8.01 (d, 2H), 8.24 (dd,

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1H), 8.66 (d, 1H), 10.58 (s, 1H).; HPLC-MS (Method A): m/z = 376 (M+H)<sup>+</sup>; Rt = 2.81 min.

### Example 377

4-Hydroxy-piperidine-1-carboxylic acid 5-(3-methoxy-benzoylamino)-pyridin-2-yl ester

5

Starting from N-(6-hydroxy-pyridin-3-yl)-3-methoxy-benzamide (0.49 g, 2.00 mmol) and using the procedure as described in Example 376 yielded the title compound (347 mg, 47% yield).

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ = 1.51 (m, 2H), 1.82 (m, 2H), 3.16 (m, 1H), 3.30 (m, 1H), 3.79 (s, 3H + m, 2H), 3.92 (m, 1H), 4.28 (br.s, 1H), 6.98 (m, 2H), 7.30 (t, 1H), 7.47 (m, 2H), 8.24 (dd, 1H), 8.64 (d, 1H), 10.04 (s, 1H); HPLC-MS (Method A): m/z = 372 (M+H)<sup>+</sup>; Rt = 2.58 min.

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### Example 378

4-Hydroxy-piperidine-1-carboxylic acid 5-(4-methoxy-benzoylamino)-pyridin-2-yl ester

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Starting from N-(6-hydroxy-pyridin-3-yl)-4-methoxy-benzamide (0.49 g, 2.00 mmol) and using the procedure as described in Example 376 yielded the title compound (297 mg, 40% yield).

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 1.61 (m, 2H), 1.92 (m, 2H), 3.25 (m, 1H), 3.39 (m, 1H), 3.89 (s, 3H + m, 3H), 4.03 (m, 1H), 6.96 (d, 2H), 7.06 (d, 1H), 7.98 (d, 2H), 8.34 (dd, 1H), 8.67 (d, 1H), 9.72 (s, 1H); HPLC-MS (Method A): m/z = 372 (M+H)<sup>+</sup>; Rt = 2.53 min.

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### Example 379

4-Hydroxy-piperidine-1-carboxylic acid 5-(2,4-dichloro-benzoylamino)-pyridin-2-yl ester

25 Starting from 2,4-dichloro-N-(6-hydroxy-pyridin-3-yl)-benzamide (0.49 g, 2.00 mmol) and using the procedure as described in Example 376 yielded the title compound (367 mg, 45% yield).

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 1.62 (m, 2H), 1.90 (m, 2H), 3.24 (m, 1H), 3.39 (m, 1H), 3.88 (m, 3H), 4.01 (m, 1H), 7.03 (d, 1H), 7.32 (d, 1H), 7.47 (s, 1H), 7.53 (d, 1H), 8.28 (dd, 1H), 8.58 (d, 1H), 10.1 (s, 1H); HPLC-MS (Method A): m/z = 410 and 412 (M+H)<sup>+</sup>; Rt = 2.99 min.

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### Example 380

4-Hydroxy-piperidine-1-carboxylic acid 5-(4-trifluoromethyl-benzoylamino)-pyridin-2-yl ester

35 Starting from N-(6-hydroxy-pyridin-3-yl)-4-trifluoromethyl-benzamide (0.56 g, 2.00 mmol) and

using the procedure as described in Example 376 yielded the title compound (367 mg, 45% yield).

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 1.61 (m, 2H), 1.93 (m, 2H), 3.27 (m, 1H), 3.41 (m, 1H), 3.67 (br.s, 1H), 3.91 (m, 2H), 4.05 (m, 1H), 7.08 (d, 1H), 7.74 (d, 2H), 8.14 (d, 2H), 8.37 (dd, 1H),  
5 8.67 (d, 1H), 10.11 (s, 1H); HPLC-MS (Method A): m/z = 410 (M+H)<sup>+</sup>; Rt = 3.18 min.

### Example 381

4-Hydroxy-piperidine-1-carboxylic acid 4,4-dimethyl-2,6-dioxo-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-6'-yl ester

10

A solution of 6'-hydroxy-4,4-dimethyl-4,5-dihydro-3H-[1,3']bipyridinyl-2,6-dione (468 mg, 2.00 mmol), 4-(tert-butyl-dimethyl-silanyloxy)-piperidine-1-carboxylic acid 5-benzoylamino-pyridin-2-yl ester (0.90 g, 2.00 mmol) and triethylamine (0.20 g, 2.00 mmol) in dimethylformamide (10 mL) was stirred at room temperature for 18 hours. The solvent was evaporated in vacuo.

15 The residue was dissolved in ethyl acetate, filtered over a short pad of silicagel and washed with ethyl acetate. The solvent was evaporated in vacuo and the residue was dissolved in 1N HCl in ethyl acetate (10 mL, 10.0 mmol). After stirring for 1.5 hours at room temperature the solvent was evaporated in vacuo. The white solid was washed with a small amount of ethyl acetate and diethyl ether and dissolved in a few millilitres of dichloromethane and triethyl-  
20 amine (1 mL). Purification by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:acetone 90:10) yielded the title compound (182 mg, 25% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 1.22 (s, 6H), 1.61 (m, 2H), 1.92 (m, 2H), 2.70 (s, 4H), 3.28 (m, 1H), 3.40 (m, 1H), 3.63 (d, 1H), 3.84-4.08 (m, 3H), 7.21 (d, 1H), 7.51 (dd, 1H), 8.07 (d, 1H); HPLC-MS (Method A): m/z = 362 (M+H)<sup>+</sup>; Rt = 2.25 min.

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### Example 382

Methyl-phenyl-carbamic acid 2,6-dioxo-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-6'-yl ester

A solution of N-methyl-N-phenyl carbamoyl chloride (170 mg, 1.00 mmol), 6'-hydroxy-4,5-dihydro-3H-[1,3]bipyridinyl-2,6-dione (206 mg, 1.00 mmol) and 1,4-diazabicyclo[2,2,2]octane (112 mg, 1.00 mmol) in tetrahydrofuran (10 mL) was stirred at room temperature for 18 hours. The solvent was evaporated in vacuo and the residue was purified by flash column chromatography (SiO<sub>2</sub>, first ethyl acetate:heptane 75:25 followed by pure ethyl acetate). Evaporation of the solvent yielded the title compound (260 mg, 77% yield) as a white solid.

35 <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 2.10 (quintet, 2H), 2.81 (t, 4H), 3.53 (br.s, 3H), 7.12 (br.s,

1H), 7.27 (m, 1H), 7.38 (m, 4H), 7.50 (d, 1H), 8.09 (s, 1H); HPLC-MS (Method A):  $m/z$  = 340 (M+H)<sup>+</sup>; Rt = 2.89 min.

**Example 383**

## 5 Methyl-phenyl-carbamic acid 5-(2,5-dioxo-pyrrolidin-1-yl)-pyridin-2-yl ester

A solution of N-methyl-N-phenyl carbamoyl chloride (170 mg, 1.00 mmol), 1-(6-hydroxy-pyridin-3-yl)-pyrrolidine-2,5-dione (192 mg, 1.00 mmol) and 1,4-diazabicyclo[2,2,2]octane (112 mg, 1.00 mmol) in tetrahydrofuran (10 mL) was stirred at room temperature for 4 hours.

- 10 The solvent was evaporated in vacuo and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane 80:20) yielding the title compound (275 mg, 85% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>):  $\delta$  = 2.89 (s, 4H), 3.44 (br.s, 3H), 7.14 (br.s, 1H), 7.27 (m, 1H), 7.39 (m, 4H), 7.74 (br.d, 1H), 8.38 (s, 1H); HPLC-MS (Method A):  $m/z$  = 326 (M+H)<sup>+</sup>; Rt = 2.78 min.

**Example 384**

## Methyl-phenyl-carbamic acid 5-(4-trifluoromethyl-benzoylamino)-pyridin-2-yl ester

- 20 A solution of N-(6-hydroxy-pyridin-3-yl)-4-trifluoromethyl-benzamide (1.41 g, 5.00 mmol), N-methyl-N-phenylcarbamoyl chloride (0.85 g, 5.00 mmol) and 1,4-diazabicyclo[2,2,2]octane (0.56 g, 5.00 mmol) in dimethylformamide (10 mL) was stirred at room temperature overnight. The solvent was evaporated in vacuo and the residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane 50:50) yielding the title compound (1.34 g, 64% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>):  $\delta$  = 3.35 + 3.51 (2 x br.s, 3H), 6.83 (br.s, 1H), 7.24-7.42 (m, 5H), 7.60 (d, 2H), 7.98 (d, 3H), 8.33 (s, 1H), 9.03 + 9.18 (2 x br.s, 1H, NH); HPLC-MS (Method A):  $m/z$  = 416 (M+H)<sup>+</sup>; Rt = 4.14 min.

30 **Example 385**

## Methyl-phenyl-carbamic acid quinolin-6-yl ester

- A solution of 6-hydroxyquinoline (1.00 g, 6.89 mmol), N-methyl-N-phenylcarbamoyl chloride (1.17 g, 6.89 mmol) and 1,4-diazabicyclo[2,2,2]octane (0.77 g, 6.89 mmol) in dichloromethane (20 mL) was stirred at room temperature for 1.25 hours. More dichloromethane was

added and the solution was extracted with water. The organic layer was dried over sodium sulphate, filtered and evaporated in vacuo. The residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane 50:50). Evaporation of the solvent and recrystallised from ethylacetate/heptane yielded the title compound (1.33 g, 69% yield) as a white solid.

- 5 <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 3.48 (s, 3H), 7.22-7.64 (m, 8H), 8.09 (d, 2H), 8.87 (m, 1H);  
HPLC-MS (Method A): m/z = 279 (M+H)<sup>+</sup>; Rt = 2.56 min.

### Example 386

4-Hydroxy-piperidine-1-carboxylic acid 5-(5-trifluoromethyl-pyridin-2-yloxy)-pyridin-2-yl ester

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A solution of 5-(5-trifluoromethyl-pyridin-2-yloxy)-pyridin-2-ol (180 mg, 0.70 mmol), 3-[4-(tert-butyl-dimethyl-silanyloxy)-piperidine-1-carbonyl]-1-methyl-3H-imidazol-1-ium iodide (317 mg, 0.70 mmol) and triethylamine (98 µL) in acetonitrile (10 mL) was stirred at room temperature overnight. The solvent was evaporated in vacuo. The residue was redissolved in some di-  
15 chloromethane, filtered over a short pad of silicagel and washed with ethyl acetate:heptane 50:50. The solvent was evaporated in vacuo and the residue was dissolved in 3.2N HCl in ether (10 mL). After stirring for 1 hour at room temperature the solvent was evaporated in vacuo and the residue was dissolved in dichloromethane. Triethylamine (0.5 mL) was added and the solution was extracted with water. The organic layer was dried over sodium sulphate,  
20 filtered and evaporated in vacuo to yield the title compound (174 mg, 65% yield) as a thick oil.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 1.63 (m, 2H), 1.79 (br.s, 1H, OH), 1.97 (m, 2H), 3.31 (m, 1H), 3.43 (m, 1H), 3.89-4.12 (m, 3H), 7.09 (d, 1H), 7.18 (d, 1H), 7.62 (dd, 1H), 7.94 (dd, 1H), 8.23 (d, 1H), 8.39 (d, 1H); HPLC-MS (Method A): m/z = 384 (M+H)<sup>+</sup>; Rt = 3.00 min.

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### Example 387

4-Hydroxy-piperidine-1-carboxylic acid 5-(3,5-dichloro-pyridin-2-yloxy)-pyridin-2-yl ester

- 30 Starting from 5-(3,5-dichloro-pyridin-2-yloxy)-pyridin-2-ol (265 mg, 1.03 mmol) and using the procedure as described in Example 386 yielded the title compound (121 mg, 54% yield) as a thick oil.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 1.62 (m, 2H), 1.94 (m, 2H), 3.06 (br.s, 1H), 3.28 (m, 1H), 3.41 (m, 1H), 3.90 (m, 2H), 4.01 (m, 1H), 7.18 (d, 1H), 7.62 (dd, 1H), 7.79 (d, 1H), 7.94 (d, 1H), 8.22 (d, 1H).; HPLC-MS (Method A): m/z = 384 (M+H)<sup>+</sup>; Rt = 3.35 min.

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**Example 388**

Methyl-phenyl-carbamic acid 5-(4-chloro-benzoylamino)-pyridin-2-yl ester

A solution of 4-chloro-N-(6-hydroxy-pyridin-3-yl)-benzamide (0.50 g, 2.01 mmol), N-methyl-N-phenylcarbonyl chloride (0.34 g, 2.01 mmol) and 1,4-diazabicyclo[2,2,2]octane (0.22 g, 0.34 mmol) in dimethylformamide (10 mmol) was stirred at room temperature for 2 hours. Water (100 mL) was added and a thick oil was being formed. The water was decanted and the residue dissolved in dichloromethane, dried over sodium sulphate, filtered and evaporated in vacuo. Ethyl acetate was added and the solution was heated briefly (some of the compound does not dissolve). The solvent was decanted and heptane was added to it. After standing overnight, the crystals were isolated by suction, washed with heptane and dried in a vacuum oven at 45 °C. Further purification by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane 50:50), yielded the title compound (0.41 g, 53% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 3.38 (br.s, 3H), 6.84 (br.s, 1H), 7.20-7.42 (m, 7H), 7.80 (d, 2H), 7.97 (dd, 1H), 8.32 (d, 1H), 9.09 (br.s, 1H); HPLC-MS (Method A): m/z = 382 (M+H)<sup>+</sup>; Rt = 3.63 min.

**Example 389**

4 Methyl-phenyl-carbamic acid 5-(4-methoxy-benzoylamino)-pyridin-2-yl ester

A solution of N-(6-hydroxy-pyridin-3-yl)-4-methoxy-benzamide (1.22 g, 5.00 mmol), N-methyl-N-phenylcarbonyl chloride (0.85 g, 5.00 mmol) and 1,4-diazabicyclo[2,2,2]octane (0.56 g, 5.00 mmol) in dimethylformamide (20 mL) was stirred at room temperature for 2 hours. Water (100 mL) was added. The solids were isolated by suction and washed with water. Crystallisation from ethyl acetate:heptane yielded the title compound (1.08 g, 57% yield).

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 3.42 (br.s, 3H), 3.86 (s, 3H), 6.89 (d, 2H + br.s, 1H), 7.27 (m, 1H), 7.39 (m, 4H), 7.84 (d, 2H), 8.11 (dd, 1H), 8.34 (d, 1H), 8.51 (br.s, 1H); HPLC-MS (Method A): m/z = 378 (M+H)<sup>+</sup>; Rt = 3.55 min.

**Example 390**

Methyl-phenyl-carbamic acid 4,4-dimethyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-6'-yl ester

A solution of 4,4-dimethyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-6'-ol (0.86 g, 4.17 mmol), N-methyl-N-phenylcarbonyl chloride (0.71 g, 4.17 mmol) and 1,4-diazabicyclo[2,2,2]octane (0.47 g, 4.17 mmol) in dichloromethane (10 mL) was stirred at room temperature for 2 hours.

Extra dichloromethane was added and the solution was washed with water, dried over sodium sulphate, filtered and evaporated in vacuo. Crystallisation from ethyl acetate:heptane yielded the title compound (0.58 g, 41% yield)

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 0.99 (s, 6H), 1.52 (m, 4H), 3.16 (m, 4H), 3.43 (br.s, 3H), 6.92 (br.d, 1H), 7.20-7.41 (m, 6H), 7.98 (d, 1H); HPLC-MS (Method A): m/z = 340 (M+H)<sup>+</sup>; Rt = 4.21 min.

### Example 391

Methyl-phenyl-carbamic acid 2-methyl-quinolin-6-yl ester

10

A solution of 2-methylquinolin-6-ol (1.00 g, 6.28 mmol), N-methyl-N-phenylcarbamoyle chloride (1.07 g, 6.28 mmol) and 1,4-diazabicyclo[2,2,2]octane (0.70 g, 6.28 mmol) in dichloromethane (10 mL) was stirred at room temperature for 18 hours. Extra dichloromethane was added and the solution was extracted twice with water, dried over sodium sulphate and filtered. Some ethyl acetate and heptane were added and the solution was slowly evaporated in vacuo yielding the title compound (1.64 g, 89% yield) as a white solid.

15

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 2.71 (s, 3H), 3.45 (br.s, 3H), 7.25 (m, 2H), 7.40 (m, 5H), 7.54 (s, 1H), 7.98 (t, 2H); HPLC-MS (Method A): m/z = 293 (M+H)<sup>+</sup>; Rt = 2.16 min.

20

**Example 392** (General procedure 17){2-[4-(Methyl-phenyl-carbamoyloxy)-phenyl]-ethyl}-carbamic acid tert-butyl ester

Tyramin was N-Boc protected as described in J. Org. Chem, **49**, 1984, 1016. To a solution of the N-Boc protected tyramin (10 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added N-methyl-N-phenylcarbamoyle chloride (15 mmol) and DABCO (15 mmol) at room temperature. The reaction mixture was stirred for 16 hours at rt, added CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and washed with aqueous citric acid (5%) and brine. The organic phase was separated, dried (MgSO<sub>4</sub>) and evaporated to give the crude product which was purified by FC (Quad flash 40 MeOH-CH<sub>2</sub>Cl<sub>2</sub> 5:95) to give 3.45 g (93%) of the title compound as colorless crystals.

25

HPLC-MS : m/z = 393.4 (M+Na); R<sub>t</sub> = 4.44 min.

30

**Example 393** (General procedure 17)Methyl-phenyl-carbamic acid 4-(2-amino-ethyl)phenyl ester

35

{2-[4-(Methyl-phenyl-carbamoyloxy)-phenyl]-ethyl}-carbamic acid tertbutyl ester(3.7 g; 10

mmol) from above was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (90 mL). Addition of TFA (6 mL) and stirring for 4 h. The reaction mixture was evaporated to dryness and dried in vacuo at 50 °C overnight producing the title compound as a TFA salt in quantitative yield as yellow hygroscopic crystals.

5 HPLC-MS :  $m/z$  = 271.1 (M+1);  $R_t$  = 2.17 min.

**Example 394** (General procedure 17) Methyl-phenyl-carbamic acid 4-[2-(toluene-4-sulfonylamino)-ethyl]-phenyl ester

10 The title compound was prepared in 39% yield as a clear oil using toluenesulfonyl chloride as the aryl sulfonyl chloride.

HPLC-MS :  $m/z$  = 425.2 (M+1);  $R_t$  = 4.33 min.

**Example 395** (General procedure 17) Methyl-phenyl-carbamic acid 4-[2-(5-dimethylamino-naphthalene-1-sulfonylamino)-ethyl]-phenyl ester

The title compound was prepared in 29% yield as a yellow fluorescent oil using 5-dimethylamino-naphthalene-1-sulfonyl chloride as the aryl sulfonyl chloride.

HPLC-MS :  $m/z$  = 505.1 (M+1);  $R_t$  = 4.58 min.

20

**Example 396** (General procedure 17) Methyl-phenyl-carbamic acid 4-[2-(3,4-difluorobenzenesulfonylamino)-ethyl]-phenyl ester

25 The title compound was prepared in 40% yield as a clear oil using 3,4-difluorobenzenesulfonyl chloride as the aryl sulfonyl chloride.

HPLC-MS :  $m/z$  = 447.1 (M+1);  $R_t$  = 4.47 min.

**Example 397** (General procedure 17) 2-[2-[4-(Methyl-phenyl-carbamoyloxy)-phenyl]-ethylsulfamoyl]-benzoic acid methyl ester

30

The title compound was prepared in 30% yield as an oil using 2-chlorosulfonyl-benzoic acid methyl ester as the aryl sulfonyl chloride.

HPLC-MS :  $m/z$  = 469.1 (M+1);  $R_t$  = 4.37 min.

35 **Example 398** (General procedure 17) Methyl-phenyl-carbamic acid 4-[2-(2,5-dichloro-



thiophene-3-sulfonylamino)-ethyl]-phenyl ester

The title compound was prepared in 39% yield as an oil using 2,5-dichloro-thiophene-3-sulfonyl chloride as the aryl sulfonyl chloride.

5 HPLC-MS :  $m/z$  = 487.0 (M+1);  $R_t$  = 4.80 min.

**Example 399** (General procedure 17) Methyl-phenyl-carbamic acid 4-[2-(5-pyridin-2-yl-thiophene-2-sulfonylamino)-ethyl]-phenyl ester

10 The title compound was prepared in 12% yield as crystals using 5-pyridin-2-yl-thiophene-2-sulfonyl chloride as the aryl sulfonyl chloride.

HPLC-MS :  $m/z$  = 494.0 (M+1);  $R_t$  = 4.42 min.

**Example 400** (General procedure 17) Methyl-phenyl-carbamic acid 4-[2-(1-methyl-1H-imidazole-4-sulfonylamino)-ethyl]-phenyl ester

The title compound was prepared in 42% yield as a yellow oil using 1-methyl-1H-imidazole-4-sulfonyl chloride as the aryl sulfonyl chloride.

HPLC-MS :  $m/z$  = 415.1 (M+1);  $R_t$  = 3.31 min.

20

**Example 401** (General procedure 17) Methyl-phenyl-carbamic acid 4-[2-(5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonylamino)-ethyl]-phenyl

The title compound was prepared in 22% yield as an oil using 5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonyl chloride as the aryl sulfonyl chloride.

25

HPLC-MS :  $m/z$  = 463.1 (M+1);  $R_t$  = 3.91 min.

**Example 402** (General procedure 17) Methyl-phenyl-carbamic acid 4-[2-(4-nitro-benzenesulfonylamino)-ethyl]-phenyl ester

30

The title compound was prepared in 25% yield as a yellow oil using 4-nitro-benzenesulfonyl chloride as the aryl sulfonyl chloride.

HPLC-MS :  $m/z$  = 456.0 (M+1);  $R_t$  = 4.19 min.

35 **Example 403** (General procedure 17) Methyl-phenyl-carbamic acid 4-[2-(6-chloro-

imidazo[2,1-b]thiazole-5-sulfonylamino)-ethyl]-phenyl ester

The title compound was prepared in 18% yield as an oil using 6-chloro-imidazo[2,1-b]thiazole-5-sulfonyl chloride as the aryl sulfonyl chloride.

5 HPLC-MS :  $m/z$  = 490.9 (M+1);  $R_t$  = 3.90 min.

**Example 404** (General procedure 17) Methyl-phenyl-carbamic acid 4-[2-(2-trifluoromethoxy-benzenesulfonylamino)-ethyl]-phenyl ester

10 The title compound was prepared in 38% yield as an oil using 2-trifluoromethoxy-benzenesulfonyl chloride as the aryl sulfonyl chloride.

HPLC-MS :  $m/z$  = 495.1 (M+1);  $R_t$  = 4.49 min.

**Example 405** (General procedure 17)

15 Methyl-phenyl-carbamic acid 4-(2-dimethylaminosulfonylamino-ethyl)-phenyl ester

The title compound was prepared in 32% yield as an oil using dimethylaminosulfamoyl chloride as the sulfonyl chloride.

HPLC-MS :  $m/z$  = 378.1 (M+1);  $R_t$  = 3.62 min.

20

**Example 406** (General procedure 17) Methyl-phenyl-carbamic acid 4-(2-methanesulfonylamino-ethyl)-phenyl ester

25 The title compound was prepared in 22% yield as an oil using methanesulfonyl chloride as the sulfonyl chloride.

HPLC-MS :  $m/z$  = 349.0 (M+1);  $R_t$  = 3.26 min.

**Example 407** (General procedure 17) Methyl-phenyl-carbamic acid 4-[2-(6-morpholin-4-yl-pyridine-3-sulfonylamino)-ethyl]-phenyl ester

30

The title compound was prepared in 55% yield as crystals using 6-morpholin-4-yl-pyridine-3-sulfonyl chloride as the aryl sulfonyl chloride.

HPLC-MS :  $m/z$  = 497.0 (M+1);  $R_t$  = 3.90 min.

35 **Example 408** (General procedure 17) Methyl-phenyl-carbamic acid 4-[2-(6-phenoxy-pyridine-3-sulfonylamino)-ethyl]-phenyl ester

The title compound was prepared in 54% yield as crystals using 6-phenoxy-pyridine-3-sulfonyl chloride as the aryl sulfonyl chloride.

HPLC-MS :  $m/z$  = 504.4 (M+1);  $R_t$  = 4.45 min.

5 **Example 409** Methyl-phenyl-carbamic acid 4-[2-[4-(4-methyl-piperazin-1-yl)-benzenesulfonylamino]-ethyl]-phenyl ester

To a stirred solution of 1-(4-bromophenyl)-4-methylpiperazine (2.05 g, 8.0 mmol) in THF (10 mL) was added dropwise 1.57 M solution in hexanes n-BuLi (4.6 mL, 7.2 mmol) over a 5-min  
10 period at -78°C. The mixture was stirred at -78°C for 15 min. Then gaseous sulphur dioxide (ca. 5 g) was added causing an immediate precipitation. The mixture was allowed to warm to room temperature and stirred for 1 h. The precipitated lithium; 4-(4-methyl-piperazin-1-yl)-benzenesulfinate was isolated by filtration under N<sub>2</sub> (g), washed with THF (20 mL) and dried *in vacuo* providing 1.83 g (96%) of the lithium sulfinate as a solid. This lithium sulfinate (83  
15 mg, 0.34 mmol) was suspended in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) and stirred with NCS (45 mg, 0.34 mmol) for 10 min at rt. A solution of N-methyl-N-phenyl-carbamic acid 4-(2-amino-ethyl)phenyl ester as its TFA salt (0.26 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL) was added together with DIPEA (0.90 mmol). The mixture was stirred at rt for 16 h and quenched with HOAc (2 mL) and water (2 mL). Extraction with CH<sub>2</sub>Cl<sub>2</sub> and drying of the combined organic extracts gave the crude product  
20 which was purified by preparative HPLC (Gilson). This gave 54 mg (33%) of the title compound as its TFA salt as colorless crystals.

HPLC-MS :  $m/z$  = 509.0 (M+1);  $R_t$  = 2.88 min.

**Example 410** Methyl-phenyl-carbamic acid 4-[2-(4-dimethylamino-benzenesulfonylamino)-ethyl]-phenyl ester  
25

To a stirred solution of (4-bromo-phenyl)-dimethylamine (4.02 g, 20 mmol) in THF (25 mL) was added dropwise 1.57 M solution in hexanes n-BuLi (11.5 mL, 18 mmol) over a 5-min period at -78°C. The mixture was stirred at -78°C for 15 min. Then gaseous sulphur dioxide (ca. 5 g) was added causing an immediate precipitation. The mixture was allowed to warm to  
30 room temperature and stirred for 1 h. The precipitated lithium sulfinate was isolated by filtration under N<sub>2</sub> (g), washed with THF (20 mL) and dried *in vacuo* providing 2.99 g (87%) of lithium; 4-dimethylamino-benzenesulfinate as a bluegreen solid. This lithium sulfinate (65 mg, 0.34 mmol) was suspended in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) and stirred with NCS (45 mg, 0.34 mmol) for 10 min at rt. A solution of N-methyl-N-phenyl-carbamic acid 4-(2-amino-ethyl)phenyl ester as its  
35 TFA salt (0.26 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL) was added together with DIPEA (0.90 mmol). The

mixture was stirred at rt for 16 h and quenched with HOAc (2 mL) and water (2 mL). Extraction with CH<sub>2</sub>Cl<sub>2</sub> and drying of the combined organic extracts gave the crude product which was purified by preparative HPLC (Gilson). This gave 37 mg (31%) of the title compound as an oil.

5 HPLC-MS :  $m/z$  = 454.5 (M+1);  $R_t$  = 4.16 min.

**Example 411**

Methyl-phenyl-carbamic acid 4-{2-[4-(2-pyrrolidin-1-yl-ethoxy)-benzenesulfonylamino]-ethyl}-phenyl ester

10 To a stirred solution of 1-[2-(4-bromo-phenoxy)-ethyl]-pyrrolidine (6.72 g, 25 mmol) in THF (45 mL) was added dropwise 1.6 M solution in hexanes n-BuLi (14 mL, 22.4 mmol) over a 5-min period at -78°C. The mixture was stirred at -78°C for 15 min. Then gaseous sulphur dioxide (ca. 6 g) was added causing an immediate precipitation. The mixture was allowed to warm to room temperature and stirred for 1 h. The precipitated lithium sulfinate was isolated  
15 by filtration under N<sub>2</sub> (g), washed with THF (40 mL) and dried *in vacuo* providing 5.04 g (78%) of lithium; 4-(2-pyrrolidin-1-yl-ethoxy)-benzenesulfinate as a solid. This lithium sulfinate (179 mg, 0.69 mmol) was suspended in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and stirred with NCS (80 mg, 0.60 mmol) for 10 min at rt. A solution of N-methyl-N-phenyl-carbamic acid 4-(2-amino-ethyl)phenyl ester as its TFA salt (0.55 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was added together with  
20 DIPEA (2.0 mmol). The mixture was stirred at rt for 16 h and evaporated to dryness. It was then redissolved in MeCN and purified by preparative HPLC (Gilson). This gave 89 mg (25%) of the title compound as its TFA salt as a crystals.

HPLC-MS :  $m/z$  = 524.5 (M+1);  $R_t$  = 3.04 min.

25 **Example 412 (General procedure 15)**

4-(Tetrahydrofuran-2-ylmethyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(tetrahydrofuran-2-ylmethyl)-piperazine, crude yield 0.28 g  
30 (89%). The crude product was stirred with a mixture of ethyl acetate (10 ml) and a solution of sodium bicarbonate (0.05 g) in water (5 ml). The aqueous layer was extracted with ethyl acetate (10 + 5 ml), the combined organic phases were washed with brine (5 ml), dried over sodium sulfate, filtered and evaporated. The residue was triturated with heptane (3 ml), filtered  
35 and dried to give the title compound, White crystals, m.p. 98 - 100 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$

8.52 - 8.37 (br, 1H), 7.98 - 7.83 (dd, 1H), 7.25 - 7.06 (m, 4H), 7.00 (d, J = 8.5 Hz), 4.18 - 3.47 (m, 7H), 2.76 - 2.36 (m, 6H), 2.13 - 1.74 (m, 3H), 1.64 - 1.40 (m, 1H); IR (KBr):  $\nu$  1715 (C=O)  $\text{cm}^{-1}$ .

5 **Example 413** (General procedure 15)

4-Cyclopropylmethyl-piperazine-1-carboxylic acid 4-(3-chloro-5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(3-chloro-5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-cyclopropylmethyl-piperazine, yield 83%. White crystals, m.p. 254-255°C; IR (KBr):  $\nu$  1728 (C=O)  $\text{cm}^{-1}$ .

**Example 414** (General procedure 15)

4-(Tetrahydro-furan-2-ylmethyl)-piperazine-1-carboxylic acid 4-(4-trifluoromethylphenoxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(4-trifluoromethyl-phenoxy)-phenyl chloroformate and 1-(tetrahydro-furan-2-ylmethyl)-piperazine, yield 93%. White crystals, m.p. 216-217°C; IR (KBr):  $\nu$  1730 (C=O)  $\text{cm}^{-1}$ .

**Example 415** (General procedure 15)

4-Cyclohexylmethyl-piperazine-1-carboxylic acid 4-(4-trifluoromethyl-phenoxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(4-trifluoromethyl-phenoxy)-phenyl chloroformate and 1-cyclohexylmethyl-piperazine, yield 93%. White crystals, m.p. 256-258 °C; IR (KBr):  $\nu$  1715 (C=O)  $\text{cm}^{-1}$ .

**Example 416** (General procedure 15)

4-Cyclohexylmethyl-piperazine-1-carboxylic acid 4-(3-chloro-5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(3-chloro-5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-cyclohexylmethyl-piperazine, yield 76%. White crystals, m.p. 265-266 °C; IR (KBr):  $\nu$  1732 (C=O)  $\text{cm}^{-1}$ .

**Example 417** (General procedure 15)

4-Cyclopropylmethyl-piperazine-1-carboxylic acid 4-(4-trifluoromethyl-phenoxy)-phenyl ester

5 The hydrochloride of the title compound was prepared from 4-(4-trifluoromethyl-phenoxy)-phenyl chloroformate and 1-cyclopropylmethyl-piperazine, yield 43%. White crystals, m.p. 238-239 °C; IR (KBr):  $\nu$  1725 (C=O)  $\text{cm}^{-1}$ .

**Example 418** (General procedure 15)

4-(Tetrahydrofuran-2-ylmethyl)-piperazine-1-carboxylic acid 4-(3-chloro-5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

10

The hydrochloride of the title compound was prepared from 4-(3-chloro-5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(tetrahydrofuran-2-ylmethyl)-piperazine, yield 23%. White crystals, m.p. 98-100 °C; IR (KBr):  $\nu$  1731 (C=O)  $\text{cm}^{-1}$ .

15 **Example 419** (General procedure 15)

4-Naphthalen-1-ylmethyl-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

20 The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-naphthalen-1-ylmethyl-piperazine, yield 71%. White crystals, m.p. 218-219 °C; IR (KBr):  $\nu$  1713 (C=O)  $\text{cm}^{-1}$ .

**Example 420** (General procedure 15)

25 4-(2-Cyclohexyl-ethyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(2-cyclohexyl-ethyl)-piperazine, yield 90%. White crystals, m.p. 274-276 °C; IR (KBr):  $\nu$  1715 (C=O)  $\text{cm}^{-1}$ .

30

**Example 421** (General procedure 15)

4-(3-Methoxy-phenyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

35 The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(3-methoxy-phenyl)-piperazine, yield 85%. White crystals, m.p. 145-147 °C; IR (KBr):  $\nu$  1715 (C=O)  $\text{cm}^{-1}$ .

mate and 1-(3-methoxy-phenyl)-piperazine, yield 96%. White solid, m.p. 109-111 °C; IR (KBr):  $\nu$  1721 (C=O)  $\text{cm}^{-1}$ .

**Example 422** (General procedure 15)

- 5 4-Cyclopropylmethyl-piperazine-1-carboxylic acid 4-[2-(4-chloro-phenyl)-ethylcarbamoyl]-phenyl ester

The title compound was prepared from 4-[2-(4-chloro-phenyl)-ethylcarbamoyl]-phenyl chloroformate and 1-cyclopropylmethyl-piperazine, yield 18%. White crystals, m.p. 225-226 °C; IR  
10 (KBr):  $\nu$  1710 (ester C=O), 1661 (amide C=O)  $\text{cm}^{-1}$ .

**Example 423** (General procedure 15)

- 15 4-(Tetrahydro-furan-2-ylmethyl)-piperazine-1-carboxylic acid 4-[2-(4-chloro-phenyl)-ethylcarbamoyl]-phenyl ester

The title compound was prepared from 4-[2-(4-chloro-phenyl)-ethylcarbamoyl]-phenyl chloroformate and 1-(tetrahydrofuran-2-ylmethyl)-piperazine, yield 12%. White crystals, m.p. 220-221 °C; IR (KBr):  $\nu$  1708 (ester C=O), 1660 (amide C=O)  $\text{cm}^{-1}$ .

- 20 **Example 424** (General procedure 15)

4-(3,4-Dichloro-benzyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(3,4-dichloro-benzyl)-piperazine, yield 86%. White crystals, m.p. 229-230 °C; IR (KBr):  $\nu$  1717 (C=O)  $\text{cm}^{-1}$ .  
25

**Example 425** (General procedure 15)

- 30 4-Cyclopropylmethyl-[1,4]diazepane-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-cyclopropylmethyl-[1,4]diazepane, yield 61%. White crystals, m.p. 208-209 °C; IR (KBr):  $\nu$  1711 (C=O)  $\text{cm}^{-1}$ .  
35

**Example 426** (General procedure 15)

4-(2-Pyridin-2-yl-ethyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

- 5 The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(2-pyridin-2-yl-ethyl)-piperazine, yield 81%. White crystals, m.p. 281-282 °C; IR (KBr):  $\nu$  1713 (C=O)  $\text{cm}^{-1}$ .

**Example 427** (General procedure 18)

- 10 4-(Pyrazin-2-yl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(pyrazin-2-yl)-piperazine. White crystals, m.p. 160-161 °C; HPLC-MS:  $m/z$  = 446 (M+1) at  $R_t$  = 4.0 min.;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  8.60 - 8.57 (m, 1H), 8.39 - 8.36 (m, 1H), 8.27 - 8.22 (dd-like, 1H), 8.14 - 8.11 (m, 1H), 7.91 - 7.87 (d-like, 1H), 7.29 - 7.21 (m, 5H), 3.80 - 3.64 (br, 6H), 3.64 - 3.50 (br, 2H); IR (KBr):  $\nu$  1737, 1714 (C=O)  $\text{cm}^{-1}$ .

**Example 428** (General procedure 15)

- 20 4-(Benzo-isothiazol-3-yl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(benzo-isothiazol-3-yl)-piperazine. Drying on a rotary evaporator of the crude product gave the title compound as the free base. Purification by flash chromatography (silica, ethyl acetate - heptane 1:4) gave white crystals, m.p. 132-133 °C; IR (KBr):  $\nu$  1726 (C=O)  $\text{cm}^{-1}$ .

**Example 429** (General procedure 15)

- 30 4-(5-Chloro-thiophen-2-ylmethyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(5-chloro-thiophen-2-ylmethyl)-piperazine, yield 48 %. White crystals, m.p. 225 - 226 °C (from EtOH);  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  12.00 (br, 1H), 8.60 - 8.55 (1H), 8.27 - 8.21 (dd-like, 1H), 7.33 - 7.20 (m, 6H), 7.20 - 7.15 (d, 1H), 4.55 (br s, 2H),



4.40 - 4.00 (br, 2H), 3.74 - 3.27 (br, 4H + H<sub>2</sub>O); 3.27 - 2.97 (br, 2H); IR (KBr):  $\nu$  1723 (C=O) cm<sup>-1</sup>.

**Example 430** (General procedure 15)

5 4-(3-Trifluoromethyl-phenyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(3-trifluoromethyl-phenyl)-piperazine. The crude product  
10 was converted to the free base, yield 56%. White crystals, m.p. 87-88 °C; IR (KBr):  $\nu$  1719 (C=O) cm<sup>-1</sup>.

**Example 431** (General procedure 15)

15 4-(5-Chloro-2-methyl-phenyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(5-chloro-2-methyl-phenyl)-piperazine. The crude product  
20 was converted to the free base, yield 26%. White crystals; HPLC-MS: m/z = 492(M+H) at Rt = 5.5 min.; IR (KBr):  $\nu$  1722 (C=O) cm<sup>-1</sup>.

**Example 432** (General procedure 15)

25 4-(1-Methyl-piperidin-4-ylmethyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The dihydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(1-methyl-piperidin-4-ylmethyl)-piperazine, yield 6%.  
White crystals, m.p. 305-306 °C; IR (KBr):  $\nu$  1713 (C=O) cm<sup>-1</sup>.

30 **Example 433** (General procedure 15)

4-Biphenyl-4-ylmethyl-[1,4]diazepane-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-biphenyl-4-ylmethyl-[1,4]diazepane. The crude product  
35

was converted to the free base, yield 17%. White crystals, m.p. 143 °C; HPLC-MS: m/z = 548(M+H) at  $R_t$  = 3.6 min.; IR (KBr):  $\nu$  1711 (C=O)  $\text{cm}^{-1}$ .

**Example 434** (General procedure XX)

5 4-(5-Dimethylamino-naphthalene-1-sulfonyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(5-dimethylamino-naphthalene-1-sulfonyl)-piperazine and purified by flash chromatography (ethyl acetate - heptane 1:4), yield 32%. Pale crystals, HPLC-MS: m/z: 601(M+1) at  $R_t$  = 5.2 min.; m.p. °C; IR (KBr):  $\nu$  1723 (C=O)  $\text{cm}^{-1}$ .

**Example 435** (General procedure 15)

15 4-(3-Methoxy-benzyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(3-methoxy-benzyl)-piperazine, yield 99%. White crystals, m.p. 214-215 °C; HPLC-MS: m/z: 489(M+1) at  $R_t$  = 2.8 min.; IR (KBr):  $\nu$  1712 (C=O)  $\text{cm}^{-1}$ .

**Example 436** (General procedure 15)

4-(3-Fluoro-benzyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

25 The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(3-fluoro-benzyl)-piperazine, yield 77%. White crystals, m.p. 138-139 °C; HPLC-MS: m/z: 476 (M+1) at  $R_t$  = 3.0 min.; IR (KBr):  $\nu$  1714 (C=O)  $\text{cm}^{-1}$ .

**Example 437** (General procedure 18)

30 4-(3-Trifluoromethyl-pyridin-2-yl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(3-trifluoromethyl-pyridin-2-yl)-piperazine, yield 25%. White crystals, m.p. 131-132 °C; HPLC-MS: m/z: 513 (M+1) at  $R_t$  = 5.0 min.; IR (KBr):  $\nu$  1722 (C=O)  $\text{cm}^{-1}$ .

**Example 438** (General procedure 15)

4-(3-Fluorobenzyl)-piperazine-1-carboxylic acid 4-(4,6-dimethyl-pyrimidin-2-ylsulfanyl)-phenyl ester

5

The hydrochloride of the title compound was prepared from 4-(4,6-dimethyl-pyrimidin-2-ylsulfanyl)-phenyl chloroformate and 1-(3-fluorobenzyl)-piperazine. The crude product was converted to the free base, yield 48%. White crystals, m.p. 117-118 °C; HPLC-MS: m/z: 453 (M+1) at Rt = 2.6 min.; IR (KBr):  $\nu$  1714 (C=O)  $\text{cm}^{-1}$ .

10

**Example 439** (General procedure 15)

5-(4-Trifluoromethoxybenzyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylic acid 4-(5-trifluoromethylpyridin-2-yloxy)-phenyl ester

15 The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 2-(4-trifluoromethoxybenzyl)-2,5-diazabicyclo[2.2.1]heptane. The crude product was converted to the free base, yield 20%. Oil; HPLC-MS: m/z: 554 (M+1) at Rt = 3.1 min.; IR (KBr):  $\nu$  1723 (C=O)  $\text{cm}^{-1}$ .

**Example 440** (General procedure 18)

1-Oxo-1,4'-thiomorpholine-4-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and thiomorpholine 1-oxide and purified by flash chromatography (ethyl acetate), yield  
25 37%. White crystals, m.p. 156 - 157 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.47 - 8.40 (s-like, 1H), 7.94 - 7.87 (dd-like, 1H), 7.24 - 7.13 (m, 4H), 7.06 - 6.99 (d-like), 4.31 - 3.91 (m, 4H), 2.97 - 2.87 - 2.75 (m, 2H + 2H); IR (KBr):  $\nu$  1710 (C=O)  $\text{cm}^{-1}$ .

**Example 441** (General procedure 18)

30 4-(2,4-Dimethoxyphenyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(2,4-dimethoxyphenyl)-piperazine. Purified by flash chromatography (ethyl acetate - heptane 1:4), yield 69%. White crystals, m.p. 98-99 °C; HPLC-MS: m/z = 504 (M+1) at  
35

Rt = 4.0 min.; IR (KBr):  $\nu$  1733, 1712 (C=O)  $\text{cm}^{-1}$ .

**Example 442** (General procedure 15)

5-Benzyl-2,5-diazabicyclo[2.2.1]heptane-2-carboxylic acid 4-(5-trifluoromethylpyridin-2-yloxy)-phenyl ester

The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 2-benzyl-2,5-diazabicyclo[2.2.1]heptane. The crude product was converted to the free base and further purified by flash chromatography (ethyl acetate - heptane 1:4), yield 16 %. White crystals, m.p. 114-115 °C; HPLC-MS: m/z: 470 (M+1) at  $R_t$  = 2.6 min.; IR (KBr):  $\nu$  1718 (C=O)  $\text{cm}^{-1}$ .

**Example 443** (General procedure 10)

4-Aminomethyl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 4-aminomethylpiperidine. The crude product was purified by preparative HPLC (Method C) (32%, off-white crystals). HPLC-MS m/z = 396.1 (M+1),  $R_t$ : 2.65 min. purity: 86%.

**Example 444** (General procedure 10)

4-Pyrimidin-2-yl-piperazine-1-carboxylic acid 4-(5-chloro-pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(2-pyrimidinyl)-piperazine, two equivalent of diisopropylethylamine was added. The crude product was obtained by filtration of the reaction mixture. The crude product was washed with diethyl ether and subjected to column chromatography, ethyl acetate/heptane (1:3) (18%, white crystals). HPLC-MS m/z = 412.1 (M+1),  $R_t$ : 4.12 min.

**Example 445** (General procedure 12)

4-Cyclopropylmethyl-piperazine-1-carboxylic acid 4-(4,4-dimethyl-2,6-dioxo-piperidin-1-yl)-phenyl ester

The title compound was prepared from 4-(4,4-dimethyl-2,6-dioxo-piperidin-1-yl)-phenyl chloroformate and 1-cyclopropylmethyl-piperazine, preparative HPLC (Method C) (45%, off-white crystals). HPLC-MS m/z = 400.3 (M+1),  $R_t$ : 1.83 min.

**Example 446** (General procedure 12)

4-(4-Methoxy-benzyl)-piperazine-1-carboxylic acid 4-(4,4-dimethyl-2,6-dioxo-piperidin-1-yl)-phenyl ester

5

The title compound was prepared from 4-(4,4-dimethyl-2,6-dioxo-piperidin-1-yl)-phenyl chloroformate and 1-(4-methoxybenzyl)-piperazine, preparative HPLC (Method C) (54%, white crystals). HPLC-MS  $m/z$  = 466.3 ( $M+1$ ),  $R_t$ : 2.26 min.

10 **Example 447** (General procedure 12)

4-Pyridin-3-ylmethyl-piperazine-1-carboxylic acid 4-(4,4-dimethyl-2,6-dioxo-piperidin-1-yl)-phenyl ester

15 The title compound was prepared from 4-(4,4-dimethyl-2,6-dioxo-piperidin-1-yl)-phenyl chloroformate and 1-pyridin-3-ylmethyl-piperazine, hydrochloride, preparative HPLC (Method C) (75%, colourless oil). HPLC-MS  $m/z$  = 437.2 ( $M+1$ ),  $R_t$ : 1.70 min.

**Example 448** (General procedure 12)

4-(4-Methoxy-benzyl)-piperazine-1-carboxylic acid 4-(2-cyclohexyl-acetylamino)-phenyl ester

20

The title compound was prepared from 4-(2-cyclohexyl-acetylamino)-phenyl chloroformate and 1-(4-methoxybenzyl)-piperazine, preparative HPLC (Method C) (49%, white crystals). HPLC-MS  $m/z$  = 466.3 ( $M+1$ ),  $R_t$ : 2.85 min.

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**Example 449** (General procedure 12)

4-Cyclopropylmethyl-piperazine-1-carboxylic acid 4-(2-cyclohexyl-acetylamino)-phenyl ester

30 The title compound was prepared from 4-(2-cyclohexyl-acetylamino)-phenyl chloroformate and 1-cyclopropylmethyl-piperazine, preparative HPLC (methode C) (60%, off-white crystals). HPLC-MS  $m/z$  = 400.3 ( $M+1$ ),  $R_t$ : 2.42 min.

**Example 450** (General procedure 12)

4-Pyridin-3-ylmethyl-piperazine-1-carboxylic acid 4-(2-cyclohexyl-acetylamino)-phenyl ester

35

The title compound was prepared from 4-(2-cyclohexyl-acetylamino)-phenyl chloroformate and 1-pyridin-3-ylmethyl-piperazine, hydrochloride, preparative HPLC (methode C) (64%, white crystals). HPLC-MS  $m/z$  = 437.4 (M+1), Rt: 2.38 min.

5 **Example 451** (General procedure 14)

Methyl-phenyl-carbamic acid 4-(2-cyclohexyl-ethylsulfamoyl)-phenyl ester

The title compound was prepared from N-(2-cyclohexyl-ethyl)-4-hydroxy-benzenesulfonamide and N-methyl-N-phenyl carbamoylchloride, preparative HPLC (Method  
10 C) (14%, light yellow oil). HPLC-MS  $m/z$  = 417.3 (M+1), Rt: 4.89 min.

**Example 452** (General procedure 14)

Methyl-phenyl-carbamic acid 4-(3-methyl-butylsulfamoyl)-phenyl ester

15 The title compound was prepared from 4-hydroxy-N-(3-methyl-butyl)-benzenesulfonamide and N-methyl-N-phenyl carbamoylchloride, preparative HPLC (Method C) (11%, light yellow oil). HPLC-MS  $m/z$  = 377.2 (M+1), Rt: 4.32 min.

**Example 453** (General procedure 12)

20 (6-Methoxy-pyridin-2-yl)-methyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The crude product was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 2-methoxy-6-methylaminopyridine. The reaction mixture was evaporated to  
25 dryness, dissolved in dichloromethane (100 ml) and extracted with a aqueous phosphate buffer, pH 7. The aqueous phase was extracted with dichloromethane (100 ml  $\times$  2) and the combined organic phases were dried and evaporated to dryness. The product was subjected to flash chromatography, ethyl acetate/heptane (1:7) to give the titlew product (86%, white crystals). HPLC-MS  $m/z$  = 420.4 (M+1), Rt: 5.23 min.

30

**Example 454** (General procedure 12)

4-Benzimidazol-1-yl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

35 The crude product was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate

mate and 1-piperidine-4-yl-1H-benzimidazole, 5 equivalent of diisopropylamine was added, preparative HPLC (method C) (23%, colourless crystals). HPLC-MS  $m/z$  = 483.3 (M+1), Rt: 3.14 min.

5 **Example 455** (General procedure 12)

4-Hydroxymethyl-piperidine-1-carboxylic acid 4-(2-cyclohexyl-acetylamino)-phenyl ester

The title compound was prepared from 4-(2-cyclohexyl-acetylamino)-phenyl chloroformate and 4-hydroxymethyl-piperidine, preparative HPLC (Method C) (37%, off-white crystals).

10 HPLC-MS  $m/z$  = 375.2 (M+1), Rt: 3.41 min.

**Example 456** (General procedure 12)

4-(4-Amino-phenyl)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

15

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 4-(4-aminophenyl)piperidine, hydrochloride, preparative HPLC (Method C) (30%, light yellow crystals). HPLC-MS  $m/z$  = 458.2 (M+1), Rt: 3.42 min.

20 **Example 457** (General procedure 12)

4-(Methyl-pyridin-3-ylmethyl-amino)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and methyl-piperidin-4-yl-pyridin-3-ylmethyl-amine, hydrochloride, preparative HPLC (Method C) (31%, orange oil). HPLC-MS  $m/z$  = 487.1 (M+1), Rt: 2.64 min.

25

**Example 458** (General procedure 12)

4-(2-Oxo-pyrrolidin-1-yl)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

30

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-piperidin-4-yl-pyrrolidine-2-one, hydrochloride, preparative HPLC (Method C) (55%, semi-crystalline oil). HPLC-MS  $m/z$  = 450.1 (M+1), Rt: 3.81 min.

35

**Example 459** (General procedure 12)

4-(Methyl-phenethyl-amino)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

- 5 The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and methyl-phenethyl-piperidin-4-yl-amine, hydrochloride, pr eparative HPLC (Method C) (37%, colourless oil). HPLC-MS  $m/z$  = 500.1 (M+1), Rt: 3.26 min.

**Example 460**

- 10 4-[(Benzyl-ethyl-amino)-methyl]-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

Benzyl-ethyl-piperidin-4-ylmethyl-amine (1.42 mmol) was dissolved in dichloromethane. 4-(5-Trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate (1.42 mmol, 0.451 g) (prepared from  
15 the corresponding phenol by conventional methods) was added at room temperature. The reaction mixture was stirred overnight and evaporated to dryness. The crude product was subjected to column chromatography, ethyl acetate/heptane (1:3) → Triethylamine/ethyl acetate 1:9). The fractions containing the title product, was evaporated to dryness and HCl (g) in ethyl acetate was added and stirred for 16 hours. The solution was evaporated to dryness  
20 and dried in vacu  for 16 h. to give the title product. (58%, light yellow crystals). HPLC-MS  $m/z$  = 514.1 (M+1), Rt: 3.27 min.

**Example 461** (General procedure 12)

- 25 4-[Methyl-phenethyl-amino)-methyl]-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and methyl-phenethyl-piperidin-4-ylmethyl-amine, hydrochloride, 5 equivalent of diisopropylamine was added, pr eparative HPLC (Method C) (46%, colourless crystals). HPLC-  
30 MS  $m/z$  = 514.1 (M+1), Rt: 3.31 min.

**Example 462** (General procedure 12)

4-[(Cyclohexyl-methyl-amino)-methyl]-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester



The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and cyclohexyl-methyl-piperidine-4-ylmethyl-amine, hydrochloride, 5 equivalent of diisopropylamine was added, preparative HPLC (Method C) (43%, white crystals). HPLC-MS  $m/z$  = 492.3 (M+1), Rt: 3.22 min.

5

**Example 463** (General procedure 12)

4-[(Ethyl-pyridin-4-ylmethyl-amino)-methyl]-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

- 10 The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and ethyl-piperidin-4-ylmethyl-pyridin-4-ylmethyl-amine, hydrochloride, 5 equivalent of diisopropylamine was added, preparative HPLC (Method C) (25%, off-white crystals). HPLC-MS  $m/z$  = 515.2 (M+1), Rt: 2.77 min.

- 15 **Example 464** (General procedure 12)

4-[(Benzyl-methyl-amino)-methyl]-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

- 20 The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and benzyl-methyl-piperidin-4-ylmethyl-amine, hydrochloride, 5 equivalent of diisopropylamine was added, preparative HPLC (Method C) (56%, colourless crystals). HPLC-MS  $m/z$  = 500.2 (M+1), Rt: 3.18 min.

**Example 465** (General procedure 12)

- 25 4-[(Methyl-pyridin-3-ylmethyl-amino)-methyl]-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

- 30 The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and methyl-piperidine-4-ylmethyl-pyridine-4-ylmethyl-amine, hydrochloride, 5 equivalent of diisopropylamine was added, preparative HPLC (Method C) (36%, colourless crystals). HPLC-MS  $m/z$  = 501.1 (M+1), Rt: 2.74 min.

**Example 466** (General procedure 12)

- 35 4-(1,3-Dihydro-indol-2-ylmethyl)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 2-piperidin-4-ylmethyl-2,3-dihydro-1H-isoindole, hydrochloride, 5 equivalent of diisopropylamine was added, preparative HPLC (Method C) (63%, colourless crystals).

5 HPLC-MS  $m/z$  = 498.1 ( $M+1$ ), Rt: 3.07 min.

#### Example 467

4-Benzotriazol-1-yl-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

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The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-piperidin-4-yl-1H-benzotriazole, hydrochloride, 5 equivalent of diisopropylamine was added, preparative HPLC (Method C) (7%, colourless crystals). HPLC-MS  $m/z$  = 506.2 ( $M+1$ ), Rt: 4.56 min.

15

#### Example 468 (General procedure 12)

4-[(Cyclopropylmethyl-amino)-methyl]-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

20 Cyclopropylmethyl-piperidine-4-ylmethyl-amine (0.65 mmol, 110 mg) was dissolved in dichloromethane. 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate (0.65 mmol, 0.208 g) (prepared from the corresponding phenol by conventional methods) was added at  $-15^{\circ}\text{C}$  for 15 min and stirred at room temperature overnight and evaporated to dryness. The crude product was purified by preparative HPLC (Method C) (16%, colourless crystals). HPLC-MS  
25  $m/z$  = 450.1 ( $M+1$ ), Rt: 2.98 min.

#### Example 469 (General procedure 12)

4-[Methyl-(2-pyridin-2-yl-ethyl)-amino]-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

30

The title product was prepared from methyl-piperidin-4-yl-(2-pyridin-2-yl-ethyl)-amine and 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate, 5 equivalent of diisopropylamine was added, preparative HPLC (method C) (48%, colourless oil). HPLC-MS  $m/z$  = 501.1 ( $M+1$ ), Rt: 2.77 min.

35

**Example 470** (General procedure 12)

4-(Cyclohexyl-methyl-amino)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

- 5 The title product was prepared from cyclohexyl-methyl-piperidin-4-yl-amine, dihydrochloride and 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate, 2 equivalent of diisopropylamine; dimethylformamide/ tetrahydrofuran (2:1). The reaction mixture was evaporated to dryness and the crude product extracted with ethyl acetate from an aqueous HCl solution saturated with sodium chloride, pH 1-2. The title product was crystallized from ethyl acetate  
10 during evaporation of the solvent, filtered and dried in vacuum (45%, white crystals). HPLC-MS  $m/z = 478.2$  (M+1), Rt: 3.10 min.

**Example 471** (General procedure 12)

- 4-(Isopropyl-methyl-amino)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-  
15 phenyl ester

The title product was prepared from isopropyl-methyl-piperidin-4-yl-amine, dihydrochloride and 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate; dimethylformamide as solvent, preparative HPLC (method C) (77%, light yellow oil). HPLC-MS  $m/z = 438.3$  (M+1), Rt: 2.77  
20 min.

**Example 472** (General procedure 12)

(4-Methoxy-phenyl)-methyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

- 25 The title product was prepared from N-methyl-p-anisidine and 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate, preparative HPLC (method C) (61%, off-white crystals). HPLC-MS  $m/z = 419.2$  (M+1), Rt: 4.67 min.

**Example 473** (General procedure 12)

- 30 (2-Methoxy-phenyl)-methyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title product was prepared from 2-methoxy-N-methylamine and 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate, preparative HPLC (method C) (63%, colourless oil). HPLC-MS  $m/z = 419.2$  (M+1), Rt: 4.75 min.

**Example 474** (General procedure 12)

(2-Carbamoyl-4-chloro-phenyl)-methyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester.

5 The title product was prepared from 5-chloro-2-(methylamino)-benzamide and 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate, preparative HPLC (method C) (31%, light yellow oil). HPLC-MS  $m/z$  = 466.1 (M+1), Rt: 3.99 min.

**Example 475** (General procedure 12)

10 (2-Carbamoyl-phenyl)-methyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title product was prepared from 2-(methylamino)benzamide and 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate, preparative HPLC (method C) (57%, light yellow oil). HPLC-MS  $m/z$  = 454.2 (M+Na), Rt: 3.66 min.

15 **Example 476** (General procedure 12)

(2-Chloro-phenyl)-methyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

20 The title product was prepared from 2-chlor-N-methylaniline and 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate, preparative HPLC (method C) (48%, light yellow oil). HPLC-MS  $m/z$  = 423.1 (M+1), Rt: 4.98 min.

**Example 477** (General procedure 12)

(2,4-Difluoro-phenyl)-methyl-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

25 The title product was prepared from 2,4-difluoro-N-methylaniline and 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate, preparative HPLC (method C) (37%, white crystals). HPLC-MS  $m/z$  = 425.1 (M+1), Rt: 4.90 min.

**Example 478** (General procedure 12)

30 Methyl-(2-trifluoromethoxy-phenyl)-carbamic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

35 The title product was prepared from N-methyl-2-(trifluoromethoxy)-aniline and 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate, preparative HPLC (method C) (49%, colourless oil). HPLC-MS  $m/z$  = 473.2 (M+1), Rt: 5.18 min.

**Example 479** (General procedure 13)

Methyl-phenyl-carbamic acid 4-(1,1,3,3-tetramethyl-butylcarbamoyl)-phenyl ester

- 5 The title product was prepared from tert-octylamine and 4-(methyl-phenyl-carbamoyloxy)-benzoic acid 2,5-dioxo-pyrrolidin-1-yl ester, preparative HPLC (method C) (26%, white crystals). HPLC-MS  $m/z$  = 383.5 (M+1), Rt: 4.67 min.

**Example 480** (General procedure 13)

- 10 Methyl-phenyl-carbamic acid 4-[(2-dimethylamino-ethyl)-methyl-carbamoyl]-phenyl ester

The title product was prepared from N,N,N'-trimethylethylendiamine and 4-(methyl-phenyl-carbamoyloxy)-benzoic acid 2,5-dioxo-pyrrolidin-1-yl ester, preparative HPLC (method C) (2%, colourless oil). HPLC-MS  $m/z$  = 356.2 (M+1), Rt: 2.17 min.

15

**Example 481** (General procedure 13)

Methyl-phenyl-carbamic acid 4-(cyclopropylmethyl-carbamoyl)-phenyl ester

- 20 The title product was prepared from cyclopropylmethylamine and 4-(methyl-phenyl-carbamoyloxy)-benzoic acid 2,5-dioxo-pyrrolidin-1-yl ester. The crude product was used without further purification (100%, semi-crystal oil). HPLC-MS  $m/z$  = 325.1 (M+1), Rt: 3.40 min.

**Example 482** (General procedure 13)

- 25 Methyl-phenyl-carbamic acid 4-(methyl-pyridin-3-ylmethyl-carbamoyl)-phenyl ester

- The title product was prepared from methyl-pyridin-3-ylmethyl-amine and 4-(methyl-phenyl-carbamoyloxy)-benzoic acid 2,5-dioxo-pyrrolidin-1-yl ester. The crude product was subjected to preparative HPLC (method C) (48%, clear colourless oil). HPLC-MS  $m/z$  = 376.2 (M+1),  
30 Rt: 2.37 min.

**Example 483** (General procedure 13)

Methyl-phenyl-carbamic acid 4-[(1H-benzimidazol-2-ylmethyl)-carbamoyl]-phenyl ester

- 35 The title product was prepared from C-(1H-benzimidazol-2-yl)-methylamine and 4-(methyl-

phenyl-carbamoyloxy)-benzoic acid 2,5-dioxo-pyrrolidin-1-yl ester. The crude product was subjected to preparative HPLC (method C) (8%, off-white crystals). HPLC-MS  $m/z$  = 401.1 ( $M+1$ ),  $R_t$ : 2.56 min.

5 **Example 484** (General procedure 13)

Methyl-phenyl-carbamic acid 4-[2-(4-chloro-phenyl)-ethylcarbamoyl]-phenyl ester

The title product was prepared from 2-(4-chloro-phenyl)-ethylamine and 4-(methyl-phenyl-carbamoyloxy)-benzoic acid 2,5-dioxo-pyrrolidin-1-yl ester. The crude product was subjected to preparative HPLC (method C) (39%, off-white crystals). HPLC-MS  $m/z$  = 409.2 ( $M+1$ ),  $R_t$ : 4.27 min.

**Example 485**

15 4-Cyclopropylmethyl-piperazine-1-carboxylic acid 4-(3,3-dimethyl-butylcarbamoyl)-phenyl ester

The title product was prepared from 1-cyclopropylmethylpiperazine (0.35 mmol) dissolved in dichloromethane (5 ml). 4-(3,3-dimethyl-butylcarbamoyl)-phenyl chloroformate (0.35 mmol) was added at room temperature. The reaction mixture was stirred for 16 h and evaporated to dryness and subjected to preparative HPLC (method C) (5%, white crystals). HPLC-MS  $m/z$  = 388.2 ( $M+1$ ),  $R_t$ : 2.43 min.

**Example 486**

25 4-Hydroxymethyl-piperidine-1-carboxylic acid 4-(3,3-dimethyl-butylcarbamoyl)-phenyl ester

The title product was prepared from 4-hydroxymethylpiperidine (0.35 mmol) was dissolved in dichloromethane (5 ml). Diisopropylethylamine (0.35 mmol) was added together with 4-(3,3-dimethyl-butylcarbamoyl)-phenyl chloroformate (0.35 mmol) at room temperature. The reaction mixture was stirred for 16 h and evaporated to dryness and subjected to preparative HPLC (method C). (25%, white crystals). HPLC-MS  $m/z$  = 363.3 ( $M+1$ ),  $R_t$ : 3.27 min.

**Example 487**

35 4-Pyridin-3-ylmethyl-piperazine-1-carboxylic acid 4-(3,3-dimethyl-butylcarbamoyl)-phenyl ester

The title product was prepared from 1-pyridin-3-ylmethyl-piperazine was dissolved in dichloromethane (5 ml). 4-(3,3-Dimethyl-butylcarbamoyl)-phenyl chloroformate (0.35 mmol) was added at room temperature. The reaction mixture was stirred for 16 h and evaporated to dryness and subjected to preparative HPLC (metod C) (88%, light yellow oil). HPLC-MS m/z = 425.4 (M+1), Rt: 2.33 min.

**Example 488**

4-(4-Methoxy-benzyl)-piperazine-1-carboxylic acid 4-(3,3-dimethyl-butylcarbamoyl)-phenyl ester

The title product was prepared from 1-(4-methoxy-benzyl)-piperazine (0.35 mmol) was dissolved in dichloromethane (5 ml). 4-(3,3-Dimethyl-butylcarbamoyl)-phenyl chloroformate (0.35 mmol) was added at room temperature. The reaction mixture was stirred for 16 h and evaporated to dryness and subjected to preparative HPLC (metod C). (54%, colourless semi-crystalline oil). HPLC-MS m/z = 454.3 (M+1), Rt: 2.78 min.

**Example 489**

4-(2-Pyridin-2-yl-acetyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

a) Piperazine-1,4-dicarboxylic acid tert-butyl ester 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester (General procedure 18)

The title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-tert-butoxycarbonyl-piperazin, yield 59% (recrystallized from EtOAc - heptane 1:1). White crystals, m.p. 165 - 166 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) □ 8.45 - 8.42 (m, 1H), 7.92 - 7.87 (m, dd-like, 1H), 7.21 - 7.12 (AB-system, 4H), 7.03 - 6.98 (m, d-like, 1H), 3.72 - 3.45 (br m, 8H), 1.49 (s, 9H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>) □ (ref. CDCl<sub>3</sub> 77.00 ppm):165.71, 154.56, 153.51, 150.21, 148.34, 145.43 (q, J= 4.4 Hz), 136.701 (q, J = 3 Hz), 123.65 (q, J= 271.5 Hz), 122.86, 122.24, 121.62 (q, J = 33 Hz), 11.20, 80.32, 44.38, 43.78, 44.6 - 42.3 (br), 28.36 ppm; IR (KBr) □ 1722 (C=O), 1691(C=O) cm<sup>-1</sup>.

b) Piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester hydrochloride

Piperazine-1,4-dicarboxylic acid tert-butyl ester 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

(0.12 g, 0.26 mmol) was stirred at 100 °C for 10 min in a mixture of ethanol (3 ml) and concentrated hydrochloric acid (1 ml). The solvent was removed in vacuum. The residue was stirred with toluene (10 ml) and evaporated, then stirred with ethanol and evaporated to dryness to give white crystals (0.10 g). Recrystallization from absolute ethanol gave the title compound. White  
5 crystals, 0.068 g (65%); m.p. 279 - 282 °C (decomp.); <sup>1</sup>H-NMR (DMSO)  $\delta$  9.62 (br, 2H, NH<sub>2</sub><sup>+</sup>), 8.61 - 8.55 (m, 1H), 8.29 - 8.21 (m, dd-like, 1H), 7.30 - 7.20 (m, 5H), 3.86 and 3.70 (br s, 4H), 3.19 (br s, 4H); <sup>13</sup>C-NMR (DMSO)  $\delta$  (ref DMSO 39.50 ppm): 165.51, 152.71, 149.98, 148.04, 145.20 (J = 4.4 Hz), 137.62 (J = 3.7 Hz), 123.87 (J = 271.5 Hz), 123.11, 123.39, 120.39 (J = 32.2Hz), 111.80, 42.15 and a broad signal partly overlapping with the DMSO signal. IR (KBr)  $\delta$   
10 1731, 1709 (C=O) cm<sup>-1</sup>.

c) 4-(2-Pyridin-2-yl-acetyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

15 Triethylamine (0.026 ml) was added to a stirred solution of (pyridin-2-yl)acetic acid hydrochloride (0.033 g, 0.19 mmol) in DMF (2.5 ml) at 0 °C. 1-Hydroxy-benzotriazole containing 8% of water (0.034 g) and then 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.044 g) was added and the mixture was stirred for 50 min. Piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester hydrochloride (0.070 g) in a mixture of DMF (1 ml)  
20 and triethylamine (0.032 ml) was added and stirring was continued over night at room temperature. The solvent was removed in vacuum and the residue was partitioned between dichloromethane (10 ml) and water (10 ml). The organic phase was washed with water (10 ml), dried over sodium sulfate, filtered and evaporated. The residue was triturated with ether-petroleumsether 1:1 and the (2 + 1 ml). The residue was dried to give the title compound. White  
25 solid, m.p. 143 - 146 °C; HPLC-MS m/z: IR (KBr)  $\delta$  1732 (C=O), 1643 (C=O).

**Example 490 (General procedure 15)**

4-(2-Pyridin-4-yl-ethyl)-piperazine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

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The hydrochloride of the title compound was prepared from 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate and 1-(4-pyridin-2-yl-ethyl)-piperazine. White crystals, m.p. 268 - 271 °C (decomp); IR (KBr)  $\delta$  2680, 2579, 2456 (N<sup>+</sup>-H), 1731, 1713 (C=O) cm<sup>-1</sup>; HPLC-MS m/z: 473 (M+H) Rt = 2.3 min.

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**Example 491**

Methyl-phenyl-carbamic acid 5-amino-pyridin-2-yl ester

5 A solution of methyl-phenyl-carbamic acid 5-nitro-pyridin-2-yl ester (10.41 g, 38.1 mmol) in tetrahydrofuran (100 mL) was hydrogenated in a Parr apparatus with wet 5% palladium on carbon and 20 psi hydrogen pressure. After 2 hours the solution was filtered over a short pad of Celite, washed thoroughly with ethyl acetate and evaporated in vacuo, yielding title compound (9.51 g, 103% yield) as a thick oil, which solidified upon standing.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 3.40 (br.s, 3H), 3.70 (br.s, 2H), 6.80 (br.d, 1H), 6.97 (dd, 1H),  
10 7.22 (m, 1H), 7.36 (m, 4H), 7.72 (d, 1H); HPLC-MS (Method A): m/z = 244 (M+H)<sup>+</sup>; R<sub>t</sub> = 2.28 min.

**Example 492**

Methyl-phenyl-carbamic acid 5-benzenesulfonylamino-pyridin-2-yl ester

15

Benzenesulphonyl chloride (0.18 g, 1.00 mmol), dissolved in a small amount of dichloromethane, was added dropwise to a stirred solution of methyl-phenyl-carbamic acid 5-amino-pyridin-2-yl ester (0.24 g, 1.00 mmol) and triethylamine (0.10 g, 1.00 mmol) in dichloromethane (10 mL). After stirring for 4 hours the solution was extracted with water and evaporated in  
20 vacuo. The residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane 40:60 followed by 50:50) yielding the title compound (108 mg, 23% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 3.46 (br.s, 3H), 6.82 (br.s, 1H), 7.24-7.52 (m, 9H), 7.63 (m, 3H), 7.84 (br.s, 1H); HPLC-MS (Method A): m/z = 384 (M+H)<sup>+</sup>; R<sub>t</sub> = 3.26 min.

25 **Example 493**

3,3-Dimethyl-4-[6-(methyl-phenyl-carbamoyloxy)-pyridin-3-ylcarbamoyl]-butyric acid

A solution of methyl-phenyl-carbamic acid 5-amino-pyridin-2-yl ester (243 mg, 1.00 mmol) and 3,3-dimethylglutaric anhydride (142 mg, 1.00 mmol) in dichloromethane (10 mL) was stirred at  
30 room temperature for 48 hours. Evaporation of the solvent yielded the title compound as a thick oil.

HPLC-MS (Method A): m/z = 386 (M+H)<sup>+</sup>; R<sub>t</sub> = 2.76 min.

**Example 494**

35 Piperidine-1-carboxylic acid 4,4-dimethyl-2,6-dioxo-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-6'-yl

1-Piperidinecarbonyl chloride (63 microL, 0.50 mmol) was added to a solution of 6'-hydroxy-4,4-dimethyl-4,5-dihydro-3H-[1,3']bipyridinyl-2,6-dione (117 mg, 0.50 mmol) and DABCO (56 mg, 0.50 mmol) in dimethylformamide (10 mL). After stirring for 1 hour at room temperature water was added and the solution was extracted twice with dichloromethane. The combined organic layers were dried over sodium sulphate, filtered and evaporated in vacuo. The residue was crystallised from ethyl acetate:heptane yielding the title compound (0.12 g, 69% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 1.21 (s, 6H), 1.64 (s, 6H), 2.69 (s, 4H), 3.53 (m, 2H), 3.63 (m, 2H), 7.22 (d, 1H), 7.49 (dd, 1H), 8.09 (d, 1H); HPLC-MS (Method A): m/z = 346 (M+H)<sup>+</sup>; R<sub>t</sub> = 3.12 min.

#### Example 495

2,2-Dimethyl-N-[6-(methyl-phenyl-carbamoyloxy)-pyridin-3-yl]-succinamic acid

A solution of methyl-phenyl-carbamic acid 5-amino-pyridin-2-yl ester (0.49 g, 2.00 mmol) and 2,2-dimethylsuccinic anhydride (0.26 g, 2.00 mmol) in dichloromethane (10 mL) was stirred at room temperature overnight. Evaporation of the solvent in vacuo yielded the title compound. HPLC-MS (Method A): m/z = 372 (M+H)<sup>+</sup>; R<sub>t</sub> = 2.84 min.

#### Example 496

Methyl-phenyl-carbamic acid 5-(3,3-dimethyl-2,5-dioxo-pyrrolidin-1-yl)-pyridin-2-yl ester

A mixture of thionyl chloride (0.726 mL, 10.00 mmol) and 2,2-dimethyl-N-[6-(methyl-phenyl-carbamoyloxy)-pyridin-3-yl]-succinamic acid (0.74 g, 2.00 mmol) in dichloromethane (25 mL) was stirred at room temperature for 18 hours. The solvent and excess thionyl chloride were evaporated in vacuo. The crude product was redissolved in dichloromethane (25 mL) and pyridine (316 mg, 4.00 mmol) was added. The solution was extracted with water, dried over sodium sulphate, filtered and evaporated in vacuo. The residue was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate:heptane 50:50), yielding the title compound (490 mg, 69% yield) as a white solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 1.43 (s, 6H), 2.74 (s, 2H), 3.45 (br.s, 3H), 7.14 (br.s, 1H), 7.26 (m, 1H), 7.38 (m, 4H), 7.76 (br.d, 1H), 8.39 (s, 1H); HPLC-MS (Method A): m/z = 354 (M+H)<sup>+</sup>; R<sub>t</sub> = 3.35 min.

**Example 497**

Methyl-phenyl-carbamic acid 5-[3,3-dimethyl-5-(4-methyl-piperazin-1-yl)-5-oxo-pentanoylamino]-pyridin-2-yl ester

- 5 Thionyl chloride (56 microL, 0.78 mmol) was added to a stirred solution of 3,3-dimethyl-4-[6-(methyl-phenyl-carbamoyloxy)-pyridin-3-ylcarbamoyl]-butyric acid (0.15 g, 0.39 mmol) in dichloromethane (5 mL) and 2 drops of dimethylformamide. After stirring for 10 minutes N-methylpiperazine (1 mL) was added and stirring was continued for 2 hours. The solvent was evaporated in vacuo. The residue was redissolved in dichloromethane and extracted with water,  
10 dried over sodium sulphate, filtered and evaporated in vacuo. The crude product was purified by filtration over a short column (SiO<sub>2</sub>, ethyl acetate followed by acetone) yielding the title compound (93 mg, 51% yield) as a thick oil.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 1.11 (s, 6H), 2.32 (s, 3H), 2.43 (m, 8H), 3.42 (br.s, 3H), 3.61 (m, 2H), 3.74 (m, 2H), 7.00 (br.s, 1H), 7.38 (d, 4H), 8.21 (dd, 1H), 8.47 (d, 1H), 10.90 (s, 1H);

- 15 HPLC-MS (Method A): m/z = 468 (M+H)<sup>+</sup>; R<sub>t</sub> = 2.20 min.

**Example 498**

Methyl-phenyl-carbamic acid 5-[3,3-dimethyl-4-(pyridin-3-ylcarbamoyl)-butyrylamino]-pyridin-2-yl ester

- 20 Thionylchloride (237 microl, 3.27 mmol) was added to a stirred solution of 3,3-dimethyl-4-[6-(methyl-phenyl-carbamoyloxy)-pyridin-3-ylcarbamoyl]-butyric acid (0.63 g, 1.63 mmol) in dichloromethane (10 mL). After stirring for 10 minutes the solution was divided into 4 equal portions of acid chloride. To one portion was added 2-aminopyridine (0.5 mL) and after stirring for 2  
25 hours at room temperature the crude product was purified by flash column chromatography (SiO<sub>2</sub>, ethyl acetate followed by ethyl acetate:acetone 90:10), yielding the title compound (105 mg, 56% yield).

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 1.09 (s, 6H), 2.36 (s, 2H), 2.38 (s, 2H), 3.44 (br.s, 3H), 6.95 (br.s, 1H), 7.26 (m, 2H), 7.38 (m, 4H), 8.05 (dd, 1H), 8.10 (dt, 1H), 8.30 (m, 2H), 8.67 (d, 1H);

- 30 HPLC-MS (Method A): m/z = 462 (M+H)<sup>+</sup>; R<sub>t</sub> = 2.52 min.

**Example 499**

Methyl-phenyl-carbamic acid 5-(3,3-dimethyl-5-morpholin-4-yl-5-oxo-pentanoylamino)-pyridin-2-yl ester

Thionylchloride (237 microl, 3.27 mmol) was added to a stirred solution of 3,3-dimethyl-4-[6-(methyl-phenyl-carbamoyloxy)-pyridin-3-ylcarbamoyl]-butyric acid (0.63 g, 1.63 mmol) in dichloromethane (10 mL). After stirring for 10 minutes the solution was divided into 4 equal portions of acid chloride. To one portion was added morpholine (0.5 mL) and after stirring for 2 hours at room temperature the crude product was purified by flash column chromatography (SiO<sub>2</sub>), yielding the title compound (117 mg, 63% yield).

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 1.11 (s, 6H), 2.44 (s, 4H), 3.42 (br.s, 3H), 3.59 (m, 2H), 3.70 (m, 6H), 7.00 (br.s, 1H), 7.24 (m, 1H), 7.38 (d, 4H), 8.21 (dd, 1H), 8.45 (d, 1H), 10.76 (s, 1H); HPLC-MS (Method A): m/z = 455 (M+H)<sup>+</sup>; R<sub>t</sub> = 2.87 min.

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**Example 500**

Methyl-phenyl-carbamic acid 5-[4-(2-dimethylamino-ethylcarbamoyl)-3,3-dimethylbutyrylamino]-pyridin-2-yl ester

Thionylchloride (237 microl, 3.27 mmol) was added to a stirred solution of 3,3-dimethyl-4-[6-(methyl-phenyl-carbamoyloxy)-pyridin-3-ylcarbamoyl]-butyric acid (0.63 g, 1.63 mmol) in dichloromethane (10 mL). After stirring for 10 minutes the solution was divided into 4 equal portions of acid chloride. To one portion was added N,N-dimethylethylenediamine (0.5 mL) and after stirring for 2 hours at room temperature the crude product was purified by flash column chromatography (SiO<sub>2</sub>), yielding the title compound (74 mg, 39% yield).

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ = 1.10 (s, 6H), 2.22 (s, 2H), 2.27 (s, 6H), 2.44 (m, 4H), 3.37 (m, 2H), 3.43 (br.s, 3H), 6.60 (br.t, 1H), 7.00 (br.s, 1H), 7.25 (m, 1H), 7.38 (d, 4H), 8.21 (dd, 1H), 8.46 (d, 1H), 10.70 (s, 1H); HPLC-MS (Method A): m/z = 456 (M+H)<sup>+</sup>; R<sub>t</sub> = 1.93 min.

**Example 501** (General procedure 12)

4-[Methyl-(2-pyridin-4-yl-ethyl)-amino]-piperidine-1-carboxylic acid 4-(5-trifluoromethylpyridin-2-yloxy)-phenyl ester

The title product was prepared from methyl-piperidine-4-yl-(2-pyridin-4-yl-ethyl)-amine and 4-(5-trifluoromethylpyridin-2-yloxy)-phenyl chloroformate, 3 equivalent of diisopropylamine was added, preparative HPLC (method C) (15%, colourless oil). HPLC-MS m/z = 501.4 (M+1), R<sub>t</sub>: 2.04 min.

**Example 502** (General procedure 12)

4-(Cyclopropyl-pyridin-4-ylmethyl-amino)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-

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pyridin-2-yloxy)-phenyl ester

The title product was prepared from cyclopropyl-piperidine-4-yl-pyridin-4-ylmethyl-amine and 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate, 3 equivalent of diisopropylamine was added, solvent: dimethylformamide. The crude reaction mixture was evaporated without addition of acetic acid, preparative HPLC (method C) (19%, yellow oil). HPLC-MS  $m/z$  = (M+1), Rt: 2.82 min.

**Example 503** (General procedure 12)

4-[Cyclopropyl-(2-fluoro-benzyl)-amino]-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title product was prepared from cyclopropyl-(2-fluoro-benzyl)-piperidin-4-yl-amine and 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate, 3 equivalent of diisopropylamine was added, solvent: dimethylformamide. The crude reaction mixture was evaporated without addition of acetic acid, preparative HPLC (method C) (60%, colourless oil). HPLC-MS  $m/z$  = (M+1), Rt: 3.02 min.

**Example 504** (General procedure 12)

4-(Cyclopropyl-pyridin-3-ylmethyl-amino)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title product was prepared from cyclopropyl-piperidin-4-yl-pyridin-3-ylmethyl-amine and 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate, 3 equivalent of diisopropylamine was added, solvent: dimethylformamide. The crude reaction mixture was evaporated without addition of acetic acid, preparative HPLC (method C) (26%, light brown solid). HPLC-MS  $m/z$  = (M+1) 513.3, Rt: 2.64 min.

**Example 505** (General procedure 12)

4-(Cyclopropylmethyl-pyridin-3-ylmethyl-amino)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title product was prepared from cyclopropylmethyl-piperidin-4-yl-pyridin-3-ylmethyl-amine and 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate, 3 equivalent of diisopropylamine was added, solvent: dimethylformamide. The crude reaction mixture was evaporated without addition of acetic acid, preparative HPLC (method C) (47%, off-white solid).

HPLC-MS  $m/z$  = (M+1) 513.3, Rt: 2.70 min.

**Example 506** (General procedure 12)

4-(Cyclopropylmethyl-pyridin-3-ylmethyl-amino)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title product was prepared from cyclopropylmethyl-piperidin-4-yl-pyridin-4-ylmethylamine and 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate, 3 equivalent of diisopropylamine was added, solvent: dimethylformamide. The crude reaction mixture was evaporated without addition of acetic acid, preparative HPLC (method C) (22%, off-white solid. HPLC-MS  $m/z$  = (M+1) 513.3, Rt: 2.70 min.

**Example 507** (General procedure 12)

4-(4-Hydroxy-piperidin-1-ylmethyl)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title product was prepared from 1-piperidin-4-ylmethyl-piperidine-4-ol (released from the correspondent hydrochloride by a standard procedure) and 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate, preparative HPLC (method C) (reaction performed in a mixture of dichloromethane and dimethylformamide). 1.7 M HCl in ethyl acetate was added to the pooled fractions containing the title product, and the fractions was evaporated to dryness (92%, white solid. HPLC-MS  $m/z$  = (M+1) 480.4, Rt: 2.38 min.

**Example 508** (General procedure 11)

4-{3-[1-(2-Hydroxy-ethyl)-piperidin-4-yl]-propyl}-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title product was prepared from 2-[4-(3-piperidin-4-yl-propyl)-piperidin-1-yl]-ethanol and 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate. The reaction mixture was evaporated, diethyl ether (30 ml) was added and the title product isolated by filtration, washed with diethyl ether and dried to give (67%, white solid. HPLC-MS  $m/z$  = (M+1) 536.2, Rt: 3.39 min.

**Example 509** (General procedure 12)

4-(2-Pyrrolidin-1-yl-ethyl)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl ester

The title product was prepared from 2-[4-(3-piperidin-4-yl-propyl)-piperidin-1-yl]-ethanol and 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate, preparative HPLC (method C). 1.7 M HCl in ethyl acetate was added to the pooled fractions containing the title product, and the fractions was evaporated to dryness (65%, white solid). HPLC-MS  $m/z = (M+1)$  464.1,  $R_t$ : 2.99 min.

**Example 510 (General procedure 16)**

**Methyl-o-tolyl-carbamic acid 4-iodo-pyrazol-1-yl ester**

The title compound was prepared from 1-hydroxy-4-iodopyrazole and methyl-o-tolylamine. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (40%, oil).  
HPLC-MS :  $m/z = 380.1$  ( $M+23$ );  $R_t = 4.05$  min.

**Example 511 (General procedure 16)**

**Methyl-m-tolyl-carbamic acid 4-iodo-pyrazol-1-yl ester**

The title compound was prepared from 1-hydroxy-4-iodopyrazole and methyl-m-tolylamine. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (44%, oil).  
HPLC-MS :  $m/z = 380.1$  ( $M+23$ );  $R_t = 4.13$  min.

**Example 512 (General procedure 16)**

**Methyl-p-tolyl-carbamic acid 4-iodo-pyrazol-1-yl ester**

The title compound was prepared from 1-hydroxy-4-iodopyrazole and methyl-p-tolylamine. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (55%, oil).  
HPLC-MS :  $m/z = 380.1$  ( $M+23$ );  $R_t = 4.13$  min.

**Example 513 (General procedure 16)**

**(3-Chloro-phenyl)-methyl-carbamic acid 4-iodo-pyrazol-1-yl ester**

The title compound was prepared from 1-hydroxy-4-iodopyrazole and 3-chlorophenyl-methylamine. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (54%, oil).

HPLC-MS :  $m/z$  = 399.9 (M+23);  $R_t$  = 4.28 min.

**Example 514** (General procedure 16)

(3-Fluoro-phenyl)-methyl-carbamic acid 4-iodo-pyrazol-1-yl ester

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The title compound was prepared from 1-hydroxy-4-iodopyrazole and 3-fluorophenyl-methylamine. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (51%, oil).

HPLC-MS :  $m/z$  = 384.0 (M+23);  $R_t$  = 4.00 min.

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**Example 515** (General procedure 16)

4-(3-Trifluoromethyl-pyridin-2-yl)-piperazine-1-carboxylic acid 4-iodo-pyrazol-1-yl ester

15 The title compound was prepared from 1-hydroxy-4-iodopyrazole and 1-(3-trifluoromethylpyridin-2-yl)piperazine. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (13%, oil).

HPLC-MS :  $m/z$  = 468.1 (M+1);  $R_t$  = 4.38 min.

**Example 516** (General procedure 16)

20 2,6-Dimethyl-morpholine-4-carboxylic acid 4-iodo-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-4-iodopyrazole and 2,6-dimethylmorpholin. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (11%, oil).

25 HPLC-MS :  $m/z$  = 374.0 (M+23);  $R_t$  = 3.24 min.

**Example 517** (General procedure 16)

Thiomorpholine-4-carboxylic acid 4-iodo-pyrazol-1-yl ester

30 The title compound was prepared from 1-hydroxy-4-iodopyrazole and thiomorpholin. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (27%, oil).

HPLC-MS :  $m/z$  = 340.0 (M+1);  $R_t$  = 3.22 min.

35 **Example 518** (General procedure 16)

3,5-Dimethyl-morpholine-4-carboxylic acid 4-iodo-pyrazol-1-yl ester



The title compound was prepared from 1-hydroxy-4-iodopyrazole and 3,5-dimethylmorpholin. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (15%, oil).

5 HPLC-MS :  $m/z$  = 352.0 (M+1);  $R_t$  = 3.17 min.

**Example 519** (General procedure 16)

Piperidine-1-carboxylic acid 4-iodo-pyrazol-1-yl ester

10 The title compound was prepared from 1-hydroxy-4-iodopyrazole and piperidine. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (46%, oil).  
HPLC-MS :  $m/z$  = 322.0 (M+1);  $R_t$  = 3.38 min.

**Example 520** (General procedure 16)

15 Methyl-o-tolyl-carbamic acid 2-chloro-imidazol-1-yl ester

The title compound was prepared from 1-hydroxy-2-chloroimidazole, hydrochloride and methyl-o-tolylamine. The crude product was purified by preparative HPLC (Gilson) (4%, red oil).

20 HPLC-MS :  $m/z$  = 266.0 (M);  $R_t$  = 3.28 min.

**Example 521** (General procedure 16)

(3-Fluoro-phenyl)-methyl-carbamic acid 2-chloro-imidazol-1-yl ester

25 The title compound was prepared from 1-hydroxy-2-chloroimidazole, hydrochloride and 3-fluorophenyl-methylamine. The crude product was purified by preparative HPLC (Gilson) (2%, oil).

HPLC-MS :  $m/z$  = 270.1 (M);  $R_t$  = 3.08 min.

30 **Example 522**

Methyl-phenyl-carbamic acid 4-iodo-phenyl ester

To a solution of 4-iodophenol (30 mmol) in  $\text{CH}_2\text{Cl}_2$  (100 mL) was added N-methyl-N-phenylcarbonyl chloride (27 mmol) and diisopropylethylamine (60 mmol) at room temperature. The reaction mixture was stirred for 16 hours at rt, added  $\text{CH}_2\text{Cl}_2$  (20 mL) and washed  
35 with aqueous citric acid (5%), aqueous  $\text{Na}_2\text{CO}_3$  and brine. The organic phase was dried

(MgSO<sub>4</sub>) and evaporated to give the crude product which was purified by FC (Quad flash 40 EtOAc-Heptane) to give 6.55 g (69%) of the title compound as light brown crystals.

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  3.38 (br s, 3H), 6.88 (d, 2H), 7.22-7.46 (m, 5H), 7.62 (d, 2H); HPLC-MS :  $m/z$  = 354.0 (M+1);  $R_t$  = 4.54 min.

5

**Example 523** (General procedure 20)

Methyl-phenyl-carbamic acid 4'-trifluoromethyl-biphenyl-4-yl ester

The title compound was prepared from methyl-phenyl-carbamic acid 4-iodo-phenyl ester and 4-trifluoromethylphenylboronic acid. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane 1:9) (42%, light brown crystals).

10

HPLC-MS :  $m/z$  = 372.1 (M+1);  $R_t$  = 5.19 min.

**Example 524** (General procedure 20)

15 Methyl-phenyl-carbamic acid 4'-trifluoromethoxy-biphenyl-4-yl ester

The title compound was prepared from methyl-phenyl-carbamic acid 4-iodo-phenyl ester and 4-trifluoromethoxyphenylboronic acid. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane 1:9) (17%, brown oil).

20

HPLC-MS :  $m/z$  = 388.1 (M+1);  $R_t$  = 5.27 min.

**Example 525** (General procedure 20)

Methyl-phenyl-carbamic acid 4-pyridin-3-yl-phenyl ester

25 The title compound was prepared from methyl-phenyl-carbamic acid 4-iodo-phenyl ester and pyridine-3-boronic acid. The crude product was purified by preparative HPLC (Gilson) (5%, brown oil).

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>):  $\delta$  3.46 (br s, 3H), 7.29-7.46 (m, 7H), 7.61 (d, 2H), 7.88 (dd, 1H), 8.41 (d, 1H), 8.78 (d, 1H); HPLC-MS :  $m/z$  = 305.1 (M+1);  $R_t$  = 2.99 min.

30

**Example 526** (General procedure 20)

Methyl-phenyl-carbamic acid 4-(5-chloro-thiophen-2-yl)-phenyl ester

The title compound was prepared from methyl-phenyl-carbamic acid 4-iodo-phenyl ester and 5-chloro-2-thiopheneboronic acid. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane 1:9) (53%, pink crystals).

35

<sup>1</sup>H NMR (300MHz; CDCl<sub>3</sub>): δ 3.43 (br s, 3H), 6.87 (d, 1H), 7.00 (d, 1H), 7.13 (br d, 2H), 7.26-7.48 (m, 7H); HPLC-MS : *m/z* = 344.0 (M+1); *R*<sub>t</sub> = 5.16 min.

**Example 527** (General procedure 20)

5 Methyl-phenyl-carbamic acid 4'-benzylsulfamoyl-biphenyl-4-yl ester

The title compound was prepared from methyl-phenyl-carbamic acid 4-iodo-phenyl ester and 4-benzylsulfamoylbenzeneboronic acid. The crude product was purified by preparative HPLC (Gilson) (35%, pink crystals).

10 HPLC-MS : *m/z* = 473.0 (M+1); *R*<sub>t</sub> = 4.80 min.

**Example 528**

Methyl-phenyl-carbamic acid 4-styryl-phenyl ester

15 Styrene (1.2 mmol), N-methyldicyclohexylamine (1.2 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (0.03 mmol), Pd(P(*t*-Bu)<sub>3</sub>)<sub>2</sub> (0.06 mmol) and methyl-phenyl-carbamic acid 4-iodo-phenyl ester (1.0 mmol) were added to a Schlenk tube under nitrogen. The Schlenk tube was evacuated and refilled with nitrogen five times. Then dioxane (2 mL) was added and the reaction mixture was stirred at 70 °C for 8 h. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) giving the title compound in 17% yield as colorless crystals.

20 HPLC-MS : *m/z* = 330.1 (M+1); *R*<sub>t</sub> = 5.08 min.

**Example 529**

Methyl-phenyl-carbamic acid 4-phenylethynyl-phenyl ester

25 Phenylacetylene (1.2 mmol), diisopropylamine (1.2 mmol), CuI (0.03 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (0.03 mmol), Pd(P(*t*-Bu)<sub>3</sub>)<sub>2</sub> (0.06 mmol) and methyl-phenyl-carbamic acid 4-iodo-phenyl ester (1.0 mmol) were added to a Schlenk tube under nitrogen. The Schlenk tube was evacuated and refilled with nitrogen five times. Then dioxane (2 mL) was added and the reaction mixture

30 was stirred at 70 °C for 8 h. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) giving the title compound in 41% yield as brown oil.

HPLC-MS : *m/z* = 328.1 (M+1); *R*<sub>t</sub> = 5.07 min.

**Example 530**

35 3-[4-(Methyl-phenyl-carbamoyloxy)-phenyl]-acrylic acid methyl ester

Methylacrylate (1.2 mmol), N-methyldicyclohexylamine (1.2 mmol),  $\text{Pd}_2(\text{dba})_3$  (0.03 mmol),  $\text{Pd}(\text{P}(t\text{-Bu})_3)_2$  (0.06 mmol) and methyl-phenyl-carbamic acid 4-iodo-phenyl ester (1.0 mmol) were added to a Schlenk tube under nitrogen. The Schlenk tube was evacuated and refilled with nitrogen five times. Then dioxane (2 mL) was added and the reaction mixture was stirred at 70 °C for 8 h. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) giving the title compound in 70% yield as a yellow solid.

HPLC-MS :  $m/z$  = 312.1 (M+1);  $R_t$  = 4.19 min.

**Example 531** (General procedure 8)

10 Methyl-phenyl-carbamic acid 5-phenylsulfanyl-pyrazol-1-yl ester

The title compound was prepared from 1-hydroxy-5-phenylsulfanylpurazole and N-methyl-N-phenylcarbonyl chloride. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (80%, oil).

15  $^1\text{H}$  NMR (300MHz;  $\text{CDCl}_3$ ):  $\delta$  3.36 (br s, 3H), 6.47 (d, 1H) 7.16-7.32 (m, 10H), 7.40 (d, 1H);

HPLC-MS :  $m/z$  = 326.0 (M+1);  $R_t$  = 4.42 min.

**Example 532** (General procedure 21)

Methyl-phenyl-carbamic acid 4-(toluene-4-sulfonylamino)-phenyl ester

20

The title compound was prepared in 8% yield as a clear oil using toluenesulfonyl chloride as the aryl sulfonyl chloride.

HPLC-MS :  $m/z$  = 397.1 (M+1);  $R_t$  = 4.13 min

25 **Example 533** (General procedure 21)

Methyl-phenyl-carbamic acid 4-(5-pyridin-2-yl-thiophene-2-sulfonylamino)-phenyl ester

The title compound was prepared in 7% yield as an oil using 5-pyridin-2-yl-thiophene-2-sulfonyl chloride as the aryl sulfonyl chloride.

30 HPLC-MS :  $m/z$  = 466.1 (M+1);  $R_t$  = 4.23 min.

**Example 534** (General procedure 21)

Methyl-phenyl-carbamic acid 4-(1-methyl-1H-imidazole-4-sulfonylamino)-phenyl ester

35 The title compound was prepared in 21% yield as crystals using 1-methyl-1H-imidazole-4-sulfonyl chloride as the aryl sulfonyl chloride.

HPLC-MS :  $m/z$  = 387.1 (M+1);  $R_t$  = 3.14 min.

**Example 535** (General procedure 21)

Methyl-phenyl-carbamic acid 4-(2,5-dichloro-thiophene-3-sulfonylamino)-phenyl ester

5

The title compound was prepared in 2% yield as an oil using 2,5-dichloro-thiophene-3-sulfonyl chloride as the aryl sulfonyl chloride.

HPLC-MS :  $m/z$  = 458.6 (M+1);  $R_t$  = 4.38 min.

10 **Example 536** (General procedure 21)

Methyl-phenyl-carbamic acid 4-(5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonylamino)-phenyl ester

15

The title compound was prepared in 3% yield as an oil using 5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonyl chloride as the aryl sulfonyl chloride.

HPLC-MS :  $m/z$  = 435.1 (M+1);  $R_t$  = 3.74 min.

**Example 537** (General procedure 21)

Methyl-phenyl-carbamic acid 4-(5-dimethylamino-naphthalene-1-sulfonylamino)-phenyl ester

20

The title compound was prepared in 14% yield as orange crystals using 5-dimethylamino-naphthalene-1-sulfonyl chloride as the aryl sulfonyl chloride.

HPLC-MS :  $m/z$  = 476.0 (M+1);  $R_t$  = 4.48 min.

25 **Example 538** (General procedure 21)

2-[4-(Methyl-phenyl-carbamoyloxy)-phenylsulfamoyl]-benzoic acid methyl ester

The title compound was prepared in 48% yield as a yellow oil using 2-chlorosulfonyl-benzoic acid methyl ester as the aryl sulfonyl chloride.

30

HPLC-MS :  $m/z$  = 441.1 (M+1);  $R_t$  = 4.19 min.

**Example 539** (General procedure 21)

Methyl-phenyl-carbamic acid 4-(3,4-difluoro-benzenesulfonylamino)-phenyl ester

35

The title compound was prepared in 1% yield as a clear oil using 3,4-difluoro-benzenesulfonyl chloride as the aryl sulfonyl chloride.

HPLC-MS :  $m/z$  = 419.1 (M+1);  $R_t$  = 4.23 min.

**Example 540** (General procedure 22 and 1)

Methyl-phenyl-carbamic acid 4-pyridin-2-ylmethyl-phenyl ester

5

4-Pyridin-2-ylmethyl-phenol was prepared following general procedure PVe3 using pyridine-2-carboxaldehyde. Subsequent carbamoylation using general procedure 1 ( $\text{CH}_2\text{Cl}_2$  was used as solvent) produced the crude product which was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (86%, oil).

10  $^1\text{H}$  NMR (400MHz;  $\text{CDCl}_3$ ):  $\delta$  3.40 (br s, 3H), 4.14 (s, 2H), 7.04-7.12 (m, 4H), 7.21-7.26 (m, 3H), 7.32-7.40 (m, 4H), 7.55 (t, 1H), 8.52 (d, 1H).

**Example 541** (General procedure 22 and 1)

Methyl-phenyl-carbamic acid 4-pyridin-3-ylmethyl-phenyl ester

15

4-Pyridin-3-ylmethyl-phenol was prepared following general procedure PVe3 using pyridine-3-carboxaldehyde. Subsequent carbamoylation using general procedure 1 ( $\text{CH}_2\text{Cl}_2$  was used as solvent) produced the crude product which was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (50%, oil).

20  $^1\text{H}$  NMR (400MHz;  $\text{CDCl}_3$ ):  $\delta$  3.42 (br s, 3H), 3.96 (s, 2H), 7.03-7.42 (m, 11H), 8.46 (d, 1H), 8.49 (d, 1H).

**Example 542** (General procedure 22 and 1)

Methyl-phenyl-carbamic acid 4-(4-trifluoromethyl-benzyl)-phenyl ester

25

4-(4-Trifluoromethyl-benzyl)-phenol was prepared following general procedure PVe3 using 4-trifluoromethylbenzaldehyde. Subsequent carbamoylation using general procedure 1 ( $\text{CH}_2\text{Cl}_2$  was used as solvent) produced the crude product which was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (92%, oil).

30  $^1\text{H}$  NMR (400MHz;  $\text{CDCl}_3$ ):  $\delta$  3.42 (br s, 3H), 4.00 (s, 2H), 7.06 (br s, 2H), 7.13 (d, 2H), 7.24-7.40 (m, 7H), 7.52 (d, 2H).

**Example 543** (General procedure 22 and 1)

Methyl-phenyl-carbamic acid 4-thiophen-3-ylmethyl-phenyl ester

35

4-Thiophen-3-ylmethyl-phenol was prepared following general procedure PVe3 using thio-

phene-3-carboxaldehyde. Subsequent carbamoylation using general procedure 1 ( $\text{CH}_2\text{Cl}_2$  was used as solvent) produced the crude product which was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (83%, oil).

$^1\text{H}$  NMR (400MHz;  $\text{CDCl}_3$ ):  $\delta$  3.42 (bs, 3H), 3.95 (s, 2H), 6.86-7.39 (m, 12H).

5

**Example 544** (General procedure 22 and 1)

Methyl-phenyl-carbamic acid 4-thiophen-2-ylmethyl-phenyl ester

4-Thiophen-2-ylmethyl-phenol phenol was prepared following general procedure PVe3 using  
10 thiophene-3-carboxaldehyde. Subsequent carbamoylation using general procedure 1 ( $\text{CH}_2\text{Cl}_2$  was used as solvent) produced the crude product which was purified by flash chromatography (Quad flash 12, EtOAc-heptane) (83%, oil).

$^1\text{H}$  NMR (400MHz;  $\text{CDCl}_3$ ):  $\delta$  3.40 (br s, 3H), 4.13 (s, 2H), 6.78 (dd, 1H), 6.90 (dd, 1H), 7.04 (br d, 2H), 7.13 (dd, 1H), 7.20-7.39 (m, 7H). HPLC-MS :  $m/z$  = 324.1 ( $\text{M}+1$ );  $R_t$  = 4.82 min.

15

**Example 545**

4-Hydroxy-piperidine-1-carboxylic acid 4-[2-(toluene-4-sulfonylamino)-ethyl]-phenyl ester

N-Boc protected tyramin (10 mmol), triethylamine (10 mmol) and 3-[4-(tert-Butyl-dimethyl-  
20 silanyloxy)-piperidine-1-carbonyl]-1-methyl-3H-imidazol-1-ium; iodide (10 mmol) in MeCN (25 mL) was stirred at room temperature for 16 hours. Acetonitrile was removed by evaporation and the crude product was purified by flash chromatography (Quad flash 40, EtOAc-heptane 1:2) providing 72% 4-tert-butylsilanyloxy-piperidine-1-carboxylic acid 4-(2-tert-butoxycarbonylamino-ethyl)-phenyl ester. This was deprotected by stirring with a 3.2 M solution of HCl in  $\text{Et}_2\text{O}$  (50 mL) for 3 h at rt and subsequently washed with ether to give 91% of 4-  
25 (4-hydroxy-piperidine-1-carboxyloxy)-phenyl-ammonium; chloride as a solid. This compound was N-tosylated as described for methyl-phenyl-carbamic acid 4-[2-(toluene-4-sulfonylamino)-ethyl]-phenyl ester to give the title compound in 26% yield as yellow crystals after purification by flash chromatography (Quad flash 12,  $\text{CH}_2\text{Cl}_2$ -MeOH 95:5).

30 HPLC-MS :  $m/z$  = 391.0 ( $\text{M}+1$ );  $R_t$  = 3.04 min.

**Example 546**

4-Hydroxy-piperidine-1-carboxylic acid 4-[2-(5-pyridin-2-yl-thiophene-2-sulfonylamino)-ethyl]-phenyl

35

4-(4-Hydroxy-piperidine-1-carboxyloxy)-phenyl-ammonium; chloride (see above) was N-

sulfonylated as described for methyl-phenyl-carbamic acid 4-[2-(5-pyridin-2-yl-thiophene-2-sulfonylamino)-ethyl]-phenyl ester to give the title compound in 59% yield as an oil after purification by preparative HPLC (Gilson).

HPLC-MS :  $m/z$  = 488.0 (M+1);  $R_t$  = 3.10 min.

5

#### Example 547

4-Hydroxy-piperidine-1-carboxylic acid 4-(5-pyridin-2-yl-thiophene-2-sulfonylamino)-phenyl ester

- 10 N-Boc protected 4-aminophenol (10 mmol), triethylamine (10 mmol) and 3-[4-(tert-Butyl-dimethyl-silanyloxy)-piperidine-1-carbonyl]-1-methyl-3H-imidazol-1-ium; iodide (10 mmol) in MeCN (25 mL) was stirred at room temperature for 16 hours. Acetonitrile was removed by evaporation and the crude product was purified by flash chromatography (Quad flash 40, EtOAc-heptane 1:2) providing 64% 4-tert-butylsilanyloxy-piperidine-1-carboxylic acid 4-tert-butoxycarbonylamino-phenyl ester. This was deprotected by stirring with a 3.2 M solution of
- 15 HCl in Et<sub>2</sub>O (50 mL) for 3 h at rt and subsequently washed with ether to give 91% of 4-(4-Hydroxy-piperidine-1-carboxyloxy)-phenyl-ammonium; chloride as a hygroscopic solid. This compound was N-sulfonylated as described for methyl-phenyl-carbamic acid 4-[2-(5-pyridin-2-yl-thiophene-2-sulfonylamino)-ethyl]-phenyl ester to give the title compound in 1% yield as
- 20 crystals after purification by preparative HPLC (Gilson).

HPLC-MS :  $m/z$  = 482.8 (M+1);  $R_t$  = 1.01 min.

#### Example 548

Methyl-phenyl-carbamic acid 4-[2-(4-amino-benzenesulfonylamino)-ethyl]-phenyl ester

25

Methyl-phenyl-carbamic acid 4-[2-(4-nitro-benzenesulfonylamino)-ethyl]-phenyl ester, 5% palladium on carbon, and ethanol were stirred under hydrogen at 1 bar and rt for 16 h. Filtration and removal of ethanol produced the title compound in 94% yield as an oil.

HPLC-MS :  $m/z$  = 426.1 (M+1);  $R_t$  = 3.61 min.

30

#### Example 549

Methyl-phenyl-carbamic acid 4-{2-[(pyridine-3-carbonyl)-amino]-ethyl}-phenyl ester

35

A solution of 3-pyridinecarboxylic acid (0.3 mmol), EDAC (0.36 mmol) and triethylamine (0.36 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added N-hydroxybenzotriazole and N-methyl-N-phenyl-carbamic acid 4-(2-amino-ethyl)phenyl ester as its TFA salt (0.3 mmol). The mixture was stirred



stirred 16 h at rt and purified by preparative HPLC (Gilson) to give the title compound in 15% yield as an oil.

HPLC-MS :  $m/z$  = 376.1 (M+1);  $R_t$  = 3.01 min.

5 **Example 550**

Methyl-phenyl-carbamic acid 4-[2-(2-dimethylamino-acetylamino)-ethyl]-phenyl ester

A solution of N,N-dimethylglycine, HCl (0.3 mmol), EDAC (0.36 mmol) and triethylamine (1.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) was added N-hydroxybenzoetriaizole and N-methyl-N-phenyl-carbamic acid 4-(2-amino-ethyl)phenyl ester as its TFA salt (0.3 mmol). The mixture was stirred 16 h at rt and purified by preparative HPLC (Gilson) to give the title compound in 66% yield as an oil.

HPLC-MS :  $m/z$  = 356.4 (M+1);  $R_t$  = 2.09 min.

15 **Example 551** (General procedure 23)

Methyl-phenyl-carbamic acid 2-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl ester

The title compound was prepared using methyl-phenyl-carbamic acid 4-[2-(toluene-4-sulfonylamino)-ethyl]-phenyl ester as the sulfonamide. The crude product was purified by flash chromatography (Quad flash 12, EtOAc-heptane 2:3) (71%, yellow oil).

HPLC-MS :  $m/z$  = 437.4 (M+1);  $R_t$  = 4.43 min.

**Example 552**

Methyl-phenyl-carbamic acid 4-[4-(2-pyrrolidin-1-yl-ethoxy)-benzyl]-phenyl ester

25

To a stirred solution of 1-[2-(4-bromo-phenoxy)-ethyl]-pyrrolidine (2.89 g, 10.7 mmol) in THF (30 mL) was added dropwise 1.6 M solution in hexanes n-BuLi (7 mL, 10.2 mmol) over a 5-min period at -78°C. The mixture was stirred at -78°C for 15 min before 4-trimethylsilyloxybenzaldehyde (2.08 g, 10.7 mmol) was added. The mixture was allowed to warm to rt during 20 min and quenched with water. Extraction with  $\text{CH}_2\text{Cl}_2$ , drying ( $\text{MgSO}_4$ ), filtration and evaporation provided the crude diarylmethanol which was dissolved in  $\text{CH}_2\text{Cl}_2$  (30 mL) and stirred with triethylsilane (4 mL) and TFA (5 mL) for 16 h at rt. Evaporation gave 3.0 g (84%) 4-[4-(2-pyrrolidin-1-yl-ethoxy)-benzyl]-phenol. This was carbamoylated using general procedure 1 ( $\text{CH}_2\text{Cl}_2$  was used as solvent) to give the title product after purification by preparative HPLC (Gilson) (35%, oil).

35

HPLC-MS :  $m/z$  = 431.5 (M+1);  $R_t$  = 2.93 min.

**Example 553** (General procedure 24)

4-Hydroxy-piperidine-1-carboxylic acid 4-pyridin-2-ylmethyl-phenyl ester

- 5 The title compound was prepared as its hydrochloride using 4-pyridin-2-ylmethyl-phenol as the phenol.

<sup>1</sup>H NMR (300MHz; D<sub>2</sub>O):  $\delta$  1.50 (br s, 2H), 1.90 (d, 2H), 3.04-3.27 (m, 2H), 3.78-4.08 (m, 3H), 4.41 (s, 2H), 7.07 (d, 2H), 7.30 (d, 2H), 7.79-7.85 (m, 2H), 8.40 (dt, 1H), 8.55 (d, 1H).

10 **Example 554** (General procedure 24)

4-Hydroxy-piperidine-1-carboxylic acid 4-pyridin-3-ylmethyl-phenyl ester

The title compound was prepared as its hydrochloride using 4-pyridin-3-ylmethyl-phenol as the phenol.

- 15 <sup>1</sup>H NMR (300MHz; D<sub>2</sub>O):  $\delta$  1.48 (br s, 2H), 1.90 (d, 2H), 3.03-3.26 (m, 2H), 3.80-4.05 (m, 3H), 4.18 (s, 2H), 7.03 (d, 2H), 7.25 (d, 2H), 7.40 (dd, 1H), 8.40 (d, 1H), 8.54-8.57 (m, 2H).

**Example 555** (General procedure 24)

4-Hydroxy-piperidine-1-carboxylic acid 4-(4-trifluoromethyl-benzyl)-phenyl ester

20

The title compound was prepared using 4-(4-trifluoromethyl-benzyl)-phenol as the phenol.

<sup>1</sup>H NMR (300MHz; D<sub>2</sub>O):  $\delta$  1.43-1.55 (m, 2H), 1.76-1.88 (m, 2H), 3.10-3.29 (m, 2H), 3.79-3.94 (m, 5H), 6.97 (d, 2H), 7.08 (d, 2H), 7.20 (d, 1H), 7.45 (d, 2H).

25 **Example 556** (General procedure 23)

Methyl-phenyl-carbamic acid 2-[4-(2-pyrrolidin-1-yl-ethoxy)-benzenesulfonyl]-1,2,3,4-tetrahydro-isoquinolin-7-yl ester

- 30 The title compound was prepared using methyl-phenyl-carbamic acid 4-{2-[4-(2-pyrrolidin-1-yl-ethoxy)-benzenesulfonylamino]-ethyl}-phenyl ester as the sulfonamide. The crude product was purified by preparative HPLC (Gilson) and isolated as its TFA salt (45%, foam).

HPLC-MS :  $m/z$  = 536.2 (M+1);  $R_t$  = 3.10 min.

**Example 557**

- 35 Methyl-phenyl-carbamic acid 4-{2-[(1-methyl-piperidine-4-carbonyl)-amino]-ethyl}-phenyl ester

A solution of 1-methylpiperidine-4-carboxylic acid (0.3 mmol), EDAC (0.36 mmol) and triethylamine (1.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added N-hydroxybenzotriazole and N-methyl-N-phenyl-carbamic acid 4-(2-amino-ethyl)phenyl ester as its TFA salt (0.3 mmol). The mixture  
5 was stirred 16 h at rt and purified by preparative HPLC (Gilson) to give the title compound in 5% yield as an oil.

HPLC-MS :  $m/z$  = 396.4 (M+1);  $R_t$  = 2.03 min.

**Example 558** (General procedure 23)

10 Methyl-phenyl-carbamic acid 2-(3,4-difluoro-benzenesulfonyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl ester

The title compound was prepared using methyl-phenyl-carbamic acid 4-[2-(3,4-difluoro-benzenesulfonylamino)-ethyl]-phenyl ester as the sulfonamide. The crude product was purified by preparative HPLC (Gilson) (24%, oil).  
15

HPLC-MS :  $m/z$  = 481.0 (M+23);  $R_t$  = 4.73 min.

**Example 559** (General procedure 23)

Methyl-phenyl-carbamic acid 1-methyl-2-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl ester  
20

The title compound was prepared using methyl-phenyl-carbamic acid 4-[2-(toluene-4-sulfonylamino)-ethyl]-phenyl ester as the sulfonamide and acetaldehyde in stead of formaldehyde. The crude product was purified by preparative HPLC (Gilson) (22%, brown oil).  
25

HPLC-MS :  $m/z$  = 451.5 (M+1);  $R_t$  = 4.43 min.

**Example 560** (General procedure 23)

Methyl-phenyl-carbamic acid 2-[4-(4-methyl-piperazin-1-yl)-benzenesulfonyl]-1,2,3,4-tetrahydro-isoquinolin  
30

The title compound was prepared using methyl-phenyl-carbamic acid 4-[2-[4-(4-methyl-piperazin-1-yl)-benzenesulfonylamino]-ethyl]-phenyl ester as the sulfonamide. The crude product was purified by preparative HPLC (Gilson) and isolated as its TFA salt (79%, crystals).  
35

HPLC-MS :  $m/z$  = 521.5 (M+1);  $R_t$  = 2.65 min.

**Example 561** (General procedure 23)

Methyl-phenyl-carbamic acid 1-methyl-2-[4-(4-methyl-piperazin-1-yl)-benzenesulfonyl]-1,2,3,4-tetrahydro-isoquinolin-7-yl ester

- 5 The title compound was prepared using methyl-phenyl-carbamic acid 4-{2-[4-(4-methyl-piperazin-1-yl)-benzenesulfonylamino]-ethyl}-phenyl ester as the sulfonamide and acetaldehyde in stead of formaldehyde. The crude product was purified by preparative HPLC (Gilson) (12%, brown oil).

HPLC-MS :  $m/z$  = 535.4 (M+1);  $R_t$  = 2.69 min.

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**Example 562**

3,3-Dimethyl-4-{2-[4-(methyl-phenyl-carbamoyloxy)-phenyl]-ethylcarbamoyl}-butyric acid

- A solution of 3,3-dimethylglutaric anhydride (0.3 mmol), diisopropylethylamine (0.30 mmol) and N-methyl-N-phenyl-carbamic acid 4-(2-amino-ethyl)phenyl ester as its TFA salt (0.3 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 mL) was stirred 1 h at rt. The mixture was washed with water and brine, dried and evaporated to give the title compound in 95% yield as an oil.

HPLC-MS :  $m/z$  = 413.2 (M+1);  $R_t$  = 3.20 min.

20 **Example 563**

Methyl-phenyl-carbamic acid 4-{2-[4-(4-methyl-piperazin-1-yl)-benzoylamino]-ethyl}-phenyl ester

- A solution of 4-(4-methylpiperazino)benzoic acid (0.3 mmol), EDAC (0.36 mmol) and triethylamine (1.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) was added N-hydroxybenzoetriaizole and N-methyl-N-phenyl-carbamic acid 4-(2-amino-ethyl)phenyl ester as its TFA salt (0.3 mmol). The mixture was stirred 16 h at rt and purified by preparative HPLC (Gilson) to give the title compound in 54% yield as its crystalline hydrochloride after treatment with HCl in diethyl ether.

HPLC-MS :  $m/z$  = 473.2 (M+1);  $R_t$  = 2.22 min.

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**Example 564**

Methyl-phenyl-carbamic acid 4-{2-[4-(4-methyl-piperazin-1-yl)methyl]-benzoylamino]-ethyl}-phenyl ester

- 35 A solution of 4-(4-methylpiperazinyl)methyl benzoic acid (0.3 mmol), EDAC (0.36 mmol) and triethylamine (1.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) was added N-hydroxybenzoetriaizole and N-

methyl-N-phenyl-carbamic acid 4-(2-amino-ethyl)phenyl ester as its TFA salt (0.3 mmol). The mixture was stirred 16 h at rt and purified by preparative HPLC (Gilson) to give the title compound in 25% yield as its crystalline hydrochloride after treatment with HCl in diethyl ether.. HPLC-MS :  $m/z$  = 487.3 (M+1);  $R_t$  = 2.13 min.

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**Example 565**

Methyl-phenyl-carbamic acid 4-[2-(4,4-dimethyl-2,6-dioxo-piperidin-1-yl)-ethyl]-phenyl ester

A solution of 3,3-dimethylglutaric anhydride (0.3 mmol), diisopropylethylamine (0.30 mmol) and N-methyl-N-phenyl-carbamic acid 4-(2-amino-ethyl)phenyl ester as its TFA salt (0.3 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 mL) was stirred 1 h at rt. Thionylchloride (3 mmol) was added and the mixture was stirred for 2 h at rt. Addition of ethanol (5 mL) followed by evaporation to dryness gave a crude product which was purified by flash chromatography (Quad flash 12, EtOAc-heptane 1:1). This gave the title compound in 23% yield as crystals. Furthermore 3,3-dimethyl-4-{2-[4-(methyl-phenyl-carbamoyloxy)-phenyl]-ethylcarbamoyl}-butyric acid ethyl ester could be isolated in 27% yield as an oil (see characterization below)

$^1\text{H}$  NMR (400MHz;  $\text{CDCl}_3$ ):  $\delta$  1.04 (s, 6H), 2.47 (s, 4H), 2.79 (t, 2H), 3.42 (br s, 3H), 3.97 (t, 2H), 7.03 (br d, 2H), 7.21-7.28 (m, 3H), 7.33-7.41 (m, 4H).

HPLC-MS :  $m/z$  = 395.2 (M+1);  $R_t$  = 4.23 min.

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**Example 566**

3,3-Dimethyl-4-{2-[4-(methyl-phenyl-carbamoyloxy)-phenyl]-ethylcarbamoyl}-butyric acid ethyl ester

For experimental details, see preparation of methyl-phenyl-carbamic acid 4-[2-(4,4-dimethyl-2,6-dioxo-piperidin-1-yl)-ethyl]-phenyl ester.

$^1\text{H}$  NMR (400MHz;  $\text{CDCl}_3$ ):  $\delta$  1.05 (s, 6H), 1.24 (t, 3H), 2.19 (s, 2H), 2.22 (s, 2H), 2.80 (t, 2H), 3.42 (br s, 3H), 3.50 (q, 2H), 4.1 (q, 2H), 6.53 (t, 1H), 7.03 (br d, 2H), 7.18 (d, 2H), 7.26 (t, 1H), 7.33-7.41 (m, 4H).

HPLC-MS :  $m/z$  = 441.2 (M+1);  $R_t$  = 4.11 min.

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**Example 567**

Methyl-phenyl-carbamic acid 4-hydroxymethyl-phenyl ester

To a solution of 4-hydroxymethylphenol (10 mmol) and 4-diazabicyclo[2.2.2]octane (DABCO) (10 mmol) in  $\text{CH}_2\text{Cl}_2$  (30 mL) was added N-methyl-N-phenylcarbamoyl chloride (10 mmol).

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The reaction mixture was stirred for 16 hours at rt, added  $\text{CH}_2\text{Cl}_2$  (20 mL) and washed with 1M aqueous HCl and brine. The organic phase was dried ( $\text{MgSO}_4$ ) and evaporated to give the crude product which was purified by FC (Quad flash 40 EtOAc-Heptane 1:1) to give 2.18 g (85%) of the title compound as an oil.

- 5  $^1\text{H}$  NMR (400MHz;  $\text{CDCl}_3$ ):  $\delta$  1.70 (br s, 1H), 3.40 (br s, 3H), 4.66 (s, 2H), 7.08 (br d, 2H), 7.25-7.42 (m, 7H); HPLC-MS :  $m/z$  = 258.1 (M+1);  $R_t$  = 2.99 min.

### Example 568

Methyl-phenyl-carbamic acid 4-(2-hydroxy-ethyl)-phenyl ester

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To a solution of 4-(2-Hydroxyethyl)phenol (10 mmol) and 4-diazabicyclo[2.2.2]octane (DABCO) (10 mmol) in  $\text{CH}_2\text{Cl}_2$  (30 mL) was added N-methyl-N-phenylcarbonyl chloride (10 mmol). The reaction mixture was stirred for 16 hours at rt, added  $\text{CH}_2\text{Cl}_2$  (20 mL), and washed with 1M aqueous HCl and brine. The organic phase was dried ( $\text{MgSO}_4$ ) and evaporated to give the 2.69 g (99%) of the title compound as crystals.

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$^1\text{H}$  NMR (400MHz;  $\text{CDCl}_3$ ):  $\delta$  1.52 (br s, 1H), 2.84 (t, 2H), 3.41 (br s, 3H), 3.81 (t, 2H), 7.04 (br d, 2H), 7.20 (d, 2H), 7.22-7.42 (m, 5H); HPLC-MS :  $m/z$  = 272.1 (M+1);  $R_t$  = 3.17 min.

### Example 569 (General procedure 1)

20 Methyl-phenyl-carbamic acid 4-(4-dimethylamino-pyridin-2-ylmethyl)-phenyl ester

- A solution of 2-(dimethylamino)ethanol (32 mmol) in hexane (120 mL) was cooled to  $-5^\circ\text{C}$  and n-BuLi (64 mmol) was added. After 30 min 4-(dimethylamine=pyridine) (16 mmol) was added and the red-orange mixture was stirred for further 1 h. The solution was cooled to  $-78^\circ\text{C}$  and 4-(trimethylsilyloxy)benzaldehyde (40 mmol) dissolved in hexane (80 mL) was added and the suspension was allowed to warm to rt over 20 min. The reaction mixture was quenched with water, and the aqueous phase was washed with  $\text{CH}_2\text{Cl}_2$ . The aqueous phase was evaporated to dryness, added NaI (96 mmol) and dissolved in MeCN (160 mL). Addition of trimethylsilylchloride (96 mmol) and stirring at rt for 16h. The purple reaction mixture was evaporated to dryness and treated with an aqueous solution of  $\text{Na}_2\text{SO}_3$  and pH was adjusted to 8. Extraction with  $\text{CH}_2\text{Cl}_2$  gave after evaporation 560 mg (15%) slightly impure 4-(4-dimethylamino-pyridin-2-ylmethyl)phenol as yellow crystals. This was carbamoylated using general procedure 1 ( $\text{CH}_2\text{Cl}_2$  was used as solvent) to give the title product as its hydrochloride after purification by preparative HPLC (Gilson) and treatment with HCl in  $\text{Et}_2\text{O}$  (48%, light yellow crystals).
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- 30
- 35

HPLC-MS :  $m/z$  = 362.2 (M+1);  $R_t$  = 2.27 min.

**Example 570** (General procedure 25)

Methyl-phenyl-carbamic acid 4-(4-imidazol-1-yl-phenoxy-methyl)-phenyl ester

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The title compound was prepared in 53% yield as light yellow crystals using and 4-imidazol-1-yl-phenol.  $^1\text{H}$  NMR (400MHz;  $\text{CDCl}_3$ ):  $\delta$  3.42 (br s, 3H), 5.08 (s, 2H), 7.03 (d, 2H), 7.12-7.42 (m, 15H), 7.77 (s, 1H); HPLC-MS :  $m/z$  = 400.1 (M+1);  $R_t$  = 2.62 min.

10 **Example 571** (General procedure 25)

Methyl-phenyl-carbamic acid 4-[4-(2-dimethylamino-ethyl)-phenoxy-methyl]-phenyl ester

15 The title compound was prepared in 52% yield as colorless crystals using methyl-phenyl-carbamic acid 4-hydroxymethyl-phenyl ester and 4-(2-dimethylaminoethyl)-phenol.  $^1\text{H}$  NMR (400MHz;  $\text{CDCl}_3$ ):  $\delta$  2.85 (s, 6H), 2.98-3.02 (m, 2H), 3.17-3.21 (m, 2H), 3.42 (br s, 3H), 5.02 (s, 2H), 6.90 (d, 2H), 7.12 (d, 2H), 7.25-7.43 (m, 7H); HPLC-MS :  $m/z$  = 405.2 (M+1);  $R_t$  = 2.91 min.

**Example 572** (General procedure 25)

20 Methyl-phenyl-carbamic acid 4-(pyrazol-1-yloxy-methyl)-phenyl ester

The title compound was prepared in 79% yield as an oil using and 1-hydroxypyrazole.  $^1\text{H}$  NMR (400MHz;  $\text{CDCl}_3$ ):  $\delta$  3.42 (br s, 3H), 5.26 (s, 2H), 6.03 (t, 1H), 6.95 (dd, 1H), 7.11 (br s, 2H), 7.25-7.42 (m, 8H); HPLC-MS :  $m/z$  = 324.1 (M+1);  $R_t$  = 3.58 min.

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**Example 573** (General procedure 25)

Methyl-phenyl-carbamic acid 4-(imidazol-1-yloxy-methyl)-phenyl ester

30 The title compound was prepared as its TFA salt in 87% yield as a solid using methyl-phenyl-carbamic acid 4-hydroxymethyl-phenyl ester and 1-hydroxyimidazole, hydrochloride.  $^1\text{H}$  NMR (400MHz;  $\text{CDCl}_3$ ):  $\delta$  3.42 (br s, 3H), 5.21 (s, 2H), 6.95 (s, 1H), 7.16-7.45 (m, 10H), 8.28 (br s, 1H); HPLC-MS :  $m/z$  = 324.1 (M+1);  $R_t$  = 1.92 min.

**Example 574** (General procedure 25)

35 Methyl-phenyl-carbamic acid 4-(2-oxo-2H-pyridin-1-ylmethyl)-phenyl ester

The title compound was prepared in 29% yield as an oil using methyl-phenyl-carbamic acid 4-(2-hydroxy-ethyl)-phenyl ester and 2-hydroxypyridine. In addition 50% of the isomeric methyl-phenyl-carbamic acid 4-[2-(pyridin-2-yloxy)-ethyl]-phenyl ester was isolated, see characterization below. <sup>1</sup>H NMR (400MHz; CDCl<sub>3</sub>): δ 3.05 (t, 2H), 3.41 (br s, 3H), 4.14 (s, 2H), 6.08 (t, 1H), 6.66 (d, 1H), 6.90 (dd, 1H), 7.02 (br s, 2H), 7.10 (d, 2H), 7.25-7.42 (m, 6H); HPLC-MS : *m/z* = 349.2 (M+1); *R<sub>t</sub>* = 3.04 min.

**Example 575** (General procedure 25)

Methyl-phenyl-carbamic acid 4-[2-(pyridin-2-yloxy)-ethyl]-phenyl ester

The title compound was prepared in 50% yield as an oil using methyl-phenyl-carbamic acid 4-(2-hydroxy-ethyl)-phenyl ester and 2-hydroxypyridine. In addition 29% of the isomeric methyl-phenyl-carbamic acid 4-(2-oxo-2H-pyridin-1-ylmethyl)-phenyl ester was isolated, see characterization above. <sup>1</sup>H NMR (400MHz; CDCl<sub>3</sub>): δ 3.08 (t, 2H), 3.41 (br s, 3H), 4.49 (s, 2H), 6.73 (d, 1H), 6.88 (dd, 1H), 7.05 (br d, 2H), 7.22-7.42 (m, 7H), 7.61 (dt, 1H), 8.18 (dd, 1H); HPLC-MS : *m/z* = 349.2 (M+1); *R<sub>t</sub>* = 3.97 min.

**Example 576** (General procedure 25)

Methyl-phenyl-carbamic acid 4-[2-(4-imidazol-1-yl-phenoxy)-ethyl]-phenyl ester

The title compound was prepared as its TFA salt in 62% yield as an oil using methyl-phenyl-carbamic acid 4-(2-hydroxy-ethyl)-phenyl ester and 4-imidazol-1-yl-phenol. <sup>1</sup>H NMR (400MHz; CDCl<sub>3</sub>): δ 3.11 (t, 2H), 3.42 (br s, 3H), 4.22 (s, 2H), 7.00-7.10 (m, 5H), 7.25-7.42 (m, 9H), 7.52 (s, 1H), 8.81 (s, 1H); HPLC-MS : *m/z* = 414.2 (M+1); *R<sub>t</sub>* = 2.73 min.

**Example 577** (General procedure 25)

Methyl-phenyl-carbamic acid 4-[2-[4-(2-dimethylamino-ethyl)-phenoxy]-ethyl]-phenyl ester

The title compound was prepared as its TFA salt in 92% yield as an oil using methyl-phenyl-carbamic acid 4-(2-hydroxy-ethyl)-phenyl ester and 4-(2-dimethylaminoethyl)-phenol. HPLC-MS : *m/z* = 419.2 (M+1); *R<sub>t</sub>* = 2.77 min.

**Example 578** (General procedure 25)

Methyl-phenyl-carbamic acid 4-[2-(pyrazol-1-yloxy)-ethyl]-phenyl ester

The title compound was prepared in 62% yield as an oil using methyl-phenyl-carbamic acid



4-(2-hydroxy-ethyl)-phenyl ester and 1-hydroxypyrazole.

<sup>1</sup>H NMR (400MHz; CDCl<sub>3</sub>): δ 3.02 (t, 2H), 3.42 (br s, 3H), 4.50 (t, 2H), 6.16 (t, 1H), 7.05 (br d, 2H), 7.20-7.41 (m, 9H); HPLC-MS : *m/z* = 338.2 (M+1); R<sub>t</sub> = 3.74 min.

5 **Example 579** (General procedure 25)

Methyl-phenyl-carbamic acid 4-[2-(imidazol-1-yloxy)-ethyl]-phenyl ester

The title compound was prepared as its TFA salt in 79% yield as an oil using methyl-phenyl-carbamic acid 4-(2-hydroxy-ethyl)-phenyl ester and 1-hydroxyimidazole hydrochlorid.

10 <sup>1</sup>H NMR (400MHz; CDCl<sub>3</sub>): δ 3.06 (t, 2H), 3.42 (br s, 3H), 4.52 (t, 2H), 7.08-7.42 (m, 11H), 8.53 (s, 1H); HPLC-MS : *m/z* = 338.2 (M+1); R<sub>t</sub> = 2.18 min.

**Example 580** (General procedure 1)

Methyl-phenyl-carbamic acid 4-(5-methyl-pyridin-2-ylmethyl)-phenyl ester

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To a stirred solution of 2-bromo-5-methylpyridine (3.45 g, 20 mmol) in THF (10 mL) was added dropwise 1.6 M solution in hexanes *n*-BuLi (12 mL, 19.2 mmol) over a 10-min period at -78°C. The mixture was stirred at -78°C for 2 min before 4-trimethylsilyloxybenzaldehyde (4.2 g, 21.6 mmol) dissolved in THF (10 mL) was added. The mixture was allowed to warm to  
20 -40 °C and quenched with water. The pH of the aqueous phase was adjusted to 7 which causes precipitation of 4-[hydroxy-(5-methyl-pyridin-2-yl)-methyl]phenol. This was isolated by filtration to give 1.13 g (27%) of 4-[hydroxy-(5-methyl-pyridin-2-yl)-methyl]phenol as crystals. This intermediate was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) and stirred with triethylsilane (4 mL) and TFA (5 mL) for 16 h at 50 °C. Evaporation gave 99% of 4-(5-methyl-pyridin-2-ylmethyl)phenol  
25 as a hygroscopic solid. This was carbamoylated using general procedure 1 (CH<sub>2</sub>Cl<sub>2</sub> was used as solvent and *N*-phenyl-*N*-methyl carbamoyl chlorid) to give 99% of the title product as its crystalline hydrochloride after purification by flash chromatography (Quad flash 12, EtOAc-heptane) and treatment with HCl in Et<sub>2</sub>O.

30 <sup>1</sup>H NMR (400MHz; CDCl<sub>3</sub>): δ 2.50 (s, 3H), 3.41 (br s, 3H), 4.57 (s, 2H), 7.10 (br s, 2H), 7.25-7.42 (m, 8H), 8.00 (dd, 1H), 8.46 (br s, 1H); HPLC-MS : *m/z* = 333.1 (M+1); R<sub>t</sub> = 2.60 min.

**Example 581** (General procedure 24)

4-Hydroxy-piperidine-1-carboxylic acid 4-(5-methyl-pyridin-2-ylmethyl)-phenyl ester

35 The title compound was prepared as its hydrochloride using of 4-(5-methyl-pyridin-2-

ylmethyl)phenol as the phenol.

$^1\text{H}$  NMR (300MHz;  $\text{CDCl}_3$ ):  $\delta$  1.57-1.67 (m, 3H), 1.95 (d, 2H), 2.51 (s, 3H), 3.21-3.40 (m, 2H), 3.90-4.05 (m, 3H), 4.58 (s, 2H), 7.11 (d, 2H), 7.38 (d, 2H), 7.45 (d, 1H), 8.02 (d, 1H), 8.48 (br s, 1H).

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**Example 582** (General procedure 25)

Methyl-phenyl-carbamic acid 4-(4-oxo-4H-pyridin-1-ylmethyl)-phenyl ester

The title compound was prepared in 33% yield as colorless crystals using methyl-phenyl-carbamic acid 4-hydroxymethyl-phenyl ester and 4-hydroxypyridine.  $^1\text{H}$  NMR (400MHz;  $\text{CDCl}_3$ ):  $\delta$  3.43 (br s, 3H), 4.92 (s, 2H), 6.43 (d, 2H), 7.17 (br s, 4H), 7.22-7.42 (m, 9H); HPLC-MS :  $m/z$  = 335.0 (M+1);  $R_t$  = 2.55 min.

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**Example 583** (General procedure 25)

15 Methyl-phenyl-carbamic acid 4-[2-(pyridin-3-yloxy)-ethyl]-phenyl ester

The title compound slightly contaminated with tributylphosphine oxide was prepared in 80% yield as an oil using methyl-phenyl-carbamic acid 4-(2-hydroxy-ethyl)-phenyl ester and 3-hydroxypyridine.

20  $^1\text{H}$  NMR (400MHz;  $\text{CDCl}_3$ ):  $\delta$  3.11 (t, 2H), 3.42 (br s, 3H), 4.23 (t, 2H), 7.07 (br d, 2H), 7.24-7.41 (m, 9H), 8.29 (br s, 1H), 8.40 (br s, 1H); HPLC-MS :  $m/z$  = 349.2 (M+1);  $R_t$  = 2.87 min.

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**Example 584** (General procedure 25)

Methyl-phenyl-carbamic acid 4-(2-oxo-2H-pyridin-1-ylmethyl)-phenyl ester

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The title compound was prepared in 66% yield as an oil using methyl-phenyl-carbamic acid 4-hydroxymethyl-phenyl ester and 2-hydroxypyridine.  $^1\text{H}$  NMR (400MHz;  $\text{CDCl}_3$ ):  $\delta$  3.42 (br s, 3H), 5.12 (s, 2H), 6.13 (t, 1H), 6.60 (d, 1H), 7.10 (br s, 2H), 7.22-7.41 (m, 9H); HPLC-MS :  $m/z$  = 335.2 (M+1);  $R_t$  = 2.97 min.

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**Example 585** (General procedure 25)

Methyl-phenyl-carbamic acid 4-(pyridin-3-yloxymethyl)-phenyl ester

The title compound was prepared in 43% yield as an oil using methyl-phenyl-carbamic acid 4-hydroxymethyl-phenyl ester and 3-hydroxypyridine.  $^1\text{H}$  NMR (400MHz;  $\text{CDCl}_3$ ):  $\delta$  3.44 (br

35

s, 3H), 5.12 (s, 2H), 7.17 (br s, 2H), 7.27-7.46 (m, 9H), 8.29 (br s, 1H), 8.49 (br s, 1H); HPLC-MS :  $m/z$  = 335.0 (M+1);  $R_t$  = 2.74 min.

**Example 586** (General procedure 26)

5 Methyl-phenyl-carbamic acid 4-[2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl]-phenyl ester

The title compound was prepared in 85% yield as crystals using methyl-phenyl-carbamic acid 4-(2-hydroxy-ethyl)-phenyl ester and succinimide.  $^1\text{H}$  NMR (400MHz;  $\text{CDCl}_3$ ):  $\delta$  2.65 (s, 4H), 2.86 (t, 2H), 3.41 (br s, 3H), 3.72 (t, 2H), 7.04 (br d, 2H), 7.19 (d, 2H), 7.26-7.42 (m, 5H);

10 HPLC-MS :  $m/z$  = 353.2 (M+1);  $R_t$  = 3.17 min.

**Example 587** (General procedure 26)

Methyl-phenyl-carbamic acid 4-[2-(1,3-dioxo-1,3-dihydro-pyrrolo[3,4-]pyridin-2-yl)-ethyl]-phenyl ester

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The title compound was prepared in 58% yield as crystals using methyl-phenyl-carbamic acid 4-(2-hydroxy-ethyl)-phenyl ester and 3,4-pyridinedicarboximide.  $^1\text{H}$  NMR (400MHz;  $\text{CDCl}_3$ ):  $\delta$  2.98 (t, 2H), 3.40 (br s, 3H), 3.93 (t, 2H), 7.05 (br d, 2H), 7.20-7.42 (m, 7H), 7.73 (dd, 1H), 9.06 (d, 1H), 9.12 (d, 1H); HPLC-MS :  $m/z$  = 402.1 (M+1);  $R_t$  = 3.56 min.

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**Example 588** (General procedure 26)

Methyl-phenyl-carbamic acid 4-(1-methyl-1H-imidazol-2-ylsulfanylmethyl)-phenyl ester

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The title compound was prepared as its TFA salt in 22% yield as an oil using methyl-phenyl-carbamic acid 4-hydroxymethyl-phenyl ester and 2-mercapto-1-methylimidazole.  $^1\text{H}$  NMR (400MHz;  $\text{CDCl}_3$ ):  $\delta$  3.34 (s, 3H), 3.40 (br s, 3H), 4.30 (s, 2H), 6.98 (br s, 2H), 7.08-7.11 (m, 3H), 7.27-7.42 (m, 5H), 7.48 (d, 1H); HPLC-MS :  $m/z$  = 354.1 (M+1);  $R_t$  = 2.12 min.

**Example 589** (General procedure 26)

30 Methyl-phenyl-carbamic acid 4-tetrazol-1-ylmethyl-phenyl ester

35

The title compound was prepared in 6% yield as an oil using methyl-phenyl-carbamic acid 4-hydroxymethyl-phenyl ester and tetrazole.  $^1\text{H}$  NMR (400MHz;  $\text{CDCl}_3$ ):  $\delta$  3.42 (br s, 3H), 5.57 (s, 2H), 7.17 (br s, 2H), 7.26-7.42 (m, 7H), 8.52 (s, 1H); HPLC-MS :  $m/z$  = 332.0 (M+23);  $R_t$  = 3.24 min.

**Example 590** (General procedure 26)

Methyl-phenyl-carbamic acid 4-(2,5-dioxo-pyrrolidin-1-ylmethyl)-phenyl ester

- 5 The title compound was prepared in 57% yield as beige crystals using methyl-phenyl-carbamic acid 4-hydroxymethyl-phenyl ester and succinimide.  $^1\text{H}$  NMR (400MHz;  $\text{CDCl}_3$ ):  $\delta$  2.68 (s, 4H), 3.41 (br s, 3H), 4.60 (s, 2H), 7.04 (br d, 2H), 7.23-7.41 (m, 7H); HPLC-MS :  $m/z$  = 339.1 ( $\text{M}+1$ );  $R_t$  = 3.40 min.

10 **Example 590** (General procedure 26)

Methyl-phenyl-carbamic acid 4-[2-(2-thioxo-2H-pyridin-1-yl)-ethyl]-phenyl ester

- The title compound was prepared in 25% yield as an oil using methyl-phenyl-carbamic acid 4-(2-hydroxy-ethyl)-phenyl ester and 2-mercaptopyridine. HPLC-MS :  $m/z$  = 365.2 ( $\text{M}+1$ );  $R_t$  = 4.08 min.
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**Example 591** (General procedure 26)

Methyl-phenyl-carbamic acid 4-(1,3-dioxo-1,3-dihydro-pyrrolo[3,4]pyridin-2-ylmethyl)-phenyl ester

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The title compound was prepared in 21% yield as an oil using methyl-phenyl-carbamic acid 4-hydroxymethyl-phenyl ester and 3,4-pyridinedicarboximide.  $^1\text{H}$  NMR (400MHz;  $\text{CDCl}_3$ ):  $\delta$  3.40 (br s, 3H), 4.82 (s, 2H), 7.06 (d, 2H), 7.22-7.44 (m, 8H), 7.73 (d, 1H), 9.04 (d, 1H), 9.12 (s, 1H); HPLC-MS :  $m/z$  = 388.0 ( $\text{M}+1$ );  $R_t$  = 3.80 min.

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**Example 592** (General procedure 26)

Methyl-phenyl-carbamic acid 4-[1,2,4]triazol-1-ylmethyl-phenyl ester

- The title compound was prepared as its TFA salt in 27% yield as an oil using methyl-phenyl-carbamic acid 4-hydroxymethyl-phenyl ester and 1,2,4-triazole.  $^1\text{H}$  NMR (400MHz;  $\text{CDCl}_3$ ):  $\delta$  3.42 (br s, 3H), 5.34 (s, 2H), 7.15 (br d, 2H), 7.26-7.43 (m, 7H), 8.10 (s, 1H), 8.38 (s, 1H); HPLC-MS :  $m/z$  = 309.1 ( $\text{M}+1$ );  $R_t$  = 2.74 min.
- 30

**Example 593** (General procedure 26)

- 35 Methyl-phenyl-carbamic acid 4-(2-thioxo-2H-pyridin-1-ylmethyl)-phenyl ester

The title compound was prepared in 14% yield as an oil using methyl-phenyl-carbamic acid 4-hydroxymethyl-phenyl ester and 2-mercaptopyridine. HPLC-MS :  $m/z$  = 351.1 (M+1);  $R_t$  = 3.95 min.

5

**Example 594** (General procedure 26)

Methyl-phenyl-carbamic acid 4-[2-(1-methyl-1H-imidazol-2-ylsulfanyl)-ethyl]-phenyl ester

10 The title compound was prepared as its TFA salt in 37% yield as an oil using methyl-phenyl-carbamic acid 4-(2-hydroxy-ethyl)-phenyl ester and 2-mercapto-1-methylimidazole. NMR (400MHz;  $CDCl_3$ ):  $\delta$  3.01 (t, 2H), 3.40 (br s, 3H), 3.47 (s, 1H), 3.64 (t, 2H), 6.92 (br d, 2H), 6.98 (s, 1H), 7.08 (d, 2H), 7.26-7.43 (m, 6H); HPLC-MS :  $m/z$  = 368.2 (M+1);  $R_t$  = 2.30 min.

**Example 595** (General procedure 26)

15 Methyl-phenyl-carbamic acid 4-(2-tetrazol-1-yl-ethyl)-phenyl ester

The title compound was prepared in 10% yield as an oil using methyl-phenyl-carbamic acid 4-(2-hydroxy-ethyl)-phenyl ester and tetrazole. NMR (400MHz;  $CDCl_3$ ):  $\delta$  3.19 (t, 2H), 3.40 (br s, 3H), 3.47 (s, 1H), 4.61 (t, 2H), 6.98-7.07 (m, 4H), 7.25-7.42 (m, 5H), 8.26 (s, 1H);  
20 HPLC-MS :  $m/z$  = 324.1 (M+1);  $R_t$  = 3.36 min.

**Example 596** (General procedure 26)

Methyl-phenyl-carbamic acid 4-[2-(pyrimidin-2-yloxy)-ethyl]-phenyl ester

25 The title compound was prepared in 24% yield as light yellow crystals using methyl-phenyl-carbamic acid 4-(2-hydroxy-ethyl)-phenyl ester and 2-hydroxypyrimidine. NMR (400MHz;  $CDCl_3$ ):  $\delta$  3.11 (t, 2H), 3.42 (br s, 3H), 4.54 (t, 2H), 6.93 (t, 1H), 7.05 (d, 2H), 7.25-7.42 (m, 7H), 8.51 (d, 2H); HPLC-MS :  $m/z$  = 350.2 (M+1);  $R_t$  = 2.86 min.

30 **Example 597** (General procedure 26)

Methyl-phenyl-carbamic acid 4-[2-(pyridin-4-ylsulfanyl)-ethyl]-phenyl ester

The title compound was prepared as its TFA salt in 5% yield as an oil using methyl-phenyl-carbamic acid 4-(2-hydroxy-ethyl)-phenyl ester and 4-mercaptopyridine. NMR (400MHz;  
35  $CDCl_3$ ):  $\delta$  3.07 (t, 2H), 3.36 (t, 2H), 3.44 (br s, 3H), 7.06 (br d, 2H), 7.20 (d, 2H), 7.25-7.43

(m, 7H), 8.51 (d, 2H); HPLC-MS :  $m/z$  = 365.2 (M+1);  $R_t$  = 2.53 min.

**Example 598** (General procedure 12)

4-(3-Amino-phenyl)-piperidine-1-carboxylic acid 4-(5-trifluoromethyl-pyridin2-yloxy)-phenyl ester,

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The title product was prepared from 4-(3-aminophenyl)piperidine (released from the correspondent hydrochloride by a standard procedure) and 4-(5-trifluoromethyl-pyridin-2-yloxy)-phenyl chloroformate, preparative HPLC (method C) (reaction performed in a mixture of dichloromethane and dimethylformamide, 5:3). 1.7 M HCl in ethyl acetate was added to the pooled fractions containing the title product, and the fractions was evaporated to dryness (7%, light yellow solid). HPLC-MS  $m/z$  = (M+1) 458.0,  $R_t$ : 3.09 min.

10

**Example 599** (General procedure 26)

Methyl-phenyl-carbamic acid 4-[2-(1-pyridin-3-yl-1H-imidazol-2-ylsulfanyl)-ethyl]-phenyl ester

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The title compound was prepared as its TFA salt in 5% yield as an oil using methyl-phenyl-carbamic acid 4-(2-hydroxy-ethyl)-phenyl ester and 3-(2thio-1H-imidazol-1-yl)pyridine. NMR (400MHz;  $CDCl_3$ ):  $\delta$  2.95 (t, 2H), 3.42 (br s, 2H), 3.56 (t, 3H), 6.98 (br d, 2H), 7.05 (d, 2H), 7.15 (d, 1H), 7.23-7.43 (m, 5H), 7.48 (d, 1H), 7.53 (dd, 1H), 7.70 (ddd, 1H), 8.65 (d, 1H), 8.77 (dd, 1H); HPLC-MS :  $m/z$  = 431.2 (M+1);  $R_t$  = 2.79 min.

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**Example 600** (General procedure 26)

Methyl-phenyl-carbamic acid 4-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-phenyl ester

The title compound was prepared in 39% yield as an oil using methyl-phenyl-carbamic acid 4-(2-hydroxy-ethyl)-phenyl ester and isoindole-1,3-dione. NMR (400MHz;  $CDCl_3$ ):  $\delta$  2.98 (t, 2H), 3.41 (br s, 2H), 3.89 (t, 3H), 7.04 (br d, 2H), 7.20-7.40 (m, 7H), 7.68-7.71 (m, 2H), 7.80-7.83 (m, 2H); HPLC-MS :  $m/z$  = 401.1 (M+1);  $R_t$  = 4.41 min.

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**Example 601**

4-Phenyl-piperidine-1-carboxylic acid 4-(5-methyl-pyridin-2-ylmethyl)-phenyl ester

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To a solution of 4-(5-methyl-pyridin-2-ylmethyl)phenol (0.8 mmol) prepared as described above and ethyldiisopropylamine (1.5 mmol) in  $CH_2Cl_2$  (5 mL) at -30 °C was added trichloromethyl chloroformate (1.0 mmol). The solution was stirred at -30 °C for 10 min and at reflux

35

temperature for 2 h. The solution was evaporated to dryness and redissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and cooled to 0 °C before addition of 4-phenylpiperidine (1.5 mmol). The solution was stirred at room temperature for 16 h evaporated to give the crude product which was purified by FC (Quad flash 40 CH<sub>2</sub>Cl<sub>2</sub>:Et<sub>2</sub>O:Heptane:Et<sub>3</sub>N 1:1:2:0.25 ->1:1:1:0.25) to give the title compound in 28% yield as an oil.

<sup>1</sup>H NMR (400MHz; CDCl<sub>3</sub>): δ 1.70-1.80 (m, 2H), 1.91 (br d, 2H), 2.29 (s, 3H), 2.72 (tt, 1H), 2.94 (br t, 1H), 3.08 (br t, 1H), 4.10 (s, 2H), 4.42 (br s, 1H), 7.00 (d, 1H), 7.06 (d, 2H), 7.21-7.26 (m, 5H), 7.32 (d, 2H), 7.38 (dd, 1H), 8.37 (d, 1H); HPLC-MS : *m/z* = 387.2 (M+1); R<sub>t</sub> = 2.95 min.

#### Example 602

4-(4-Methoxy-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid 4-(5-methyl-pyridin-2-ylmethyl)-phenyl ester

To a solution of 4-(5-methyl-pyridin-2-ylmethyl)phenol (0.8 mmol) prepared as described above and ethyldiisopropylamine (1.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at -30 °C was added trichloromethyl chloroformate (1.0 mmol). The solution was stirred at -30 °C for 10 min and at reflux temperature for 2 h. The solution was evaporated to dryness and redissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and cooled to 0 °C before addition of 4-(4-methoxyphenyl)-1,2,3,6-tetrahydro-pyridine (1.5 mmol). The solution was stirred at room temperature for 16 h evaporated to give the crude product which was purified by FC (Quad flash 40 CH<sub>2</sub>Cl<sub>2</sub>:Et<sub>2</sub>O:Heptane:Et<sub>3</sub>N 1:1:2:0.25 ->1:1:1:0.25) to give the title compound in 10% yield as colorless crystals.

<sup>1</sup>H NMR (400MHz; CDCl<sub>3</sub>): δ 2.30 (s, 3H), 2.60 (br s, 2H), 3.75-3.88 (m, 5H), 4.12 (s, 2H), 4.20 (br s, 1H), 4.30 (br s, 1H), 5.98 (br s, 1H), 6.88 (d, 2H), 7.00 (d, 1H), 7.07 (d, 2H), 7.24 (d, 2H), 7.34 (d, 2H), 7.39 (dd, 1H), 8.38 (d, 1H); HPLC-MS : *m/z* = 415.3 (M+1); R<sub>t</sub> = 2.95 min.

## PHARMACOLOGICAL METHODS

Compounds of formula I may be evaluated in vitro for their efficacy and potency to inhibit HSL, and such evaluation may be performed as described below.

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### ASSAYS

#### Hormone-sensitive lipase (HSL)

- 10 Materials. The Hormone-sensitive lipase was provided by Dr. Cecilia Holm, from Lund University Sweden or produced and purified by Novo Nordisk (NN) using the reagents and protocols used by Dr. Holm. The substrates used are:  $^3\text{H}$ -labeled triolein (TO) from Amersham, Buckinghamshire, U.K. cat No. TRA191; 5-20 Ci/mmol dissolved in toluene, triolein (Sigma, Cat. No. T-1740), fluorochrome-labeled triacylglyceride (*cis*-octadec-9-enoic acid 2-[12-(7-nitrobenzo[1,2,5]oxadiazol-4-ylamino)dodecanoyloxy]-1-*cis*-octadec-9-enoyloxymethyl-ethyl ester) prepared by Novo Nordisk (NN) by conventional methods, and 1,3-(di[ $^3\text{H}$ ]-stearin), 2-(PEG-Biotin)glycerol prepared in collaboration with Amersham Pharmacia Biotech, UK and described in WO 01/073442. Phosphatidyl choline (PC) and phosphatidyl inositol (PI) are from Sigma (St Luis MO cat. Nos. P-3556 and P-5954 respectively). All other reagents are of commercial grade and obtained from various commercial sources.

#### Methods.

**3180.1:** Assay for determination of inhibitor  $\text{IC}_{50}$  values.

- 25 A lipid emulsion with  $^3\text{H}$ -Triolein and phospholipid is used as substrate with a standard concentration of highly purified HSL. BSA is added as product receptor. The substrate is prepared as follows:

30  $30\ \mu\text{l}$  PC:PI (20 mg/ml solution of PC:PI 3:1 prepared in chloroform) +  $128\ \mu\text{l}$  cold TO +  $15\ \mu\text{l}$   $^3\text{H}$ -TO are mixed and then evaporated under a gentle stream of  $\text{N}_2$  followed by 20-30 minutes in a Speedvac to ensure the absence of residual solvent.

- 30 Compound and HSL are incubated for 30 min at  $25\ ^\circ\text{C}$  before addition of substrate. Reaction is stopped after 30 min at  $25\ ^\circ\text{C}$  by adding a mixture of methanol, chloroform and heptane at high pH. Formed product is separated from substrate by phase separation. Standard concentrations of compound are  $100\ \mu\text{M}$ ,  $20\ \mu\text{M}$ ,  $4\ \mu\text{M}$ ,  $0.8\ \mu\text{M}$ ,  $0.16\ \mu\text{M}$  and  $0.032\ \mu\text{M}$  (sample concentrations).

- 35 Results are given as  $\text{IC}_{50}$  values after 4PL fit of obtained activity data.



**3180.2:** Assay for determination of percent inhibition by compound at 10  $\mu$ M concentration. A lipid emulsion with  $^3$ H-Triolein and phospholipid is used as substrate with a standard concentration of highly purified HSL. BSA is added as product receptor. The substrate is prepared as follows:

- 5 30  $\mu$ l PC:PI (20 mg/ml solution of PC:PI 3:1 prepared in chloroform) + 128  $\mu$ l cold TO + 15  $\mu$ l  $^3$ H-TO are mixed and then evaporated under a gentle stream of  $N_2$  followed by 20-30 minutes in a Speedvac to ensure the absence of residual solvent.

Compound and HSL are incubated for 30 min at 25  $^{\circ}$ C before addition of substrate. Reaction is stopped after 30 min at 25  $^{\circ}$ C by adding a mixture of methanol, chloroform and heptane at high pH. Formed product is separated from substrate by phase separation.

10 Results are given as percent activity relative to an un-inhibited sample (no compound).

- 3190.1:** Assay for determination of percent inhibition of hormone sensitive lipase by compound at 10 $\mu$ M sample concentration.
- 15

A lipid emulsion with fluorochrome-labeled triacylglyceride and phospholipid is used as substrate with a standard concentration of highly purified HSL (12 $\mu$ g/mL initial concentration corresponding to 600ng/mL final concentration). BSA is added as product receptor. The transfer of the fluorochrome from the lipid phase to the water (BSA) phase changes the fluorescent properties of the fluorochrome. The changes can be monitored on a fluorimeter with an excitation wavelength of 450nm and an emission wavelength of 545nm.

20

Compound and HSL (20 $\mu$ L compound, 10 $\mu$ L enzyme and 70 $\mu$ L PED-BSA buffer) is pre-incubated for 30min at 25 $^{\circ}$ C before addition of substrate (100 $\mu$ L). Amount of formed product is measured after 120min incubation at 37 $^{\circ}$ C.

- 25 Results are given as percent activity relative to a non-inhibited sample (no compound).

- 3190.2:** Assay for determination of  $IC_{50}$  value for the inhibition of hormone sensitive lipase by compound. Standard concentrations of compound are 100 $\mu$ M and 5-fold dilutions (initial concentration corresponding to 10 $\mu$ M final concentration and 5-fold).
- 30

A lipid emulsion with fluorochrome-labeled triacylglyceride and phospholipid is used as substrate with a standard concentration of highly purified HSL (12 $\mu$ g/mL initial concentration corresponding to 600ng/mL final concentration). BSA is added as product receptor. The transfer of the fluorochrome from the lipid phase to the water (BSA) phase changes the fluorescent

properties of the fluorochrome. The changes can be monitored on a fluorimeter with an excitation wavelength of 450nm and an emission wavelength of 545nm.

Compound and HSL (20µL compound, 10µL enzyme and 70µL PED-BSA buffer) is pre-incubated for 30min at 25°C before addition of substrate (100µL). Amount of formed product is measured after 120min incubation at 37°C.

Results are given as IC<sub>50</sub> values after 4PL fit of obtained activity data.

- 2848.2: This high-volume screening assay uses para-nitrophenyl butyrate (p-NPB) as substrate for HSL. HSL cleaves p-NPB and the reaction is monitored as an increase in the concentration of para-nitrophenol (p-NP). p-NP can be monitored as an increase in UV-absorbance at 405 nm. The reaction is carried out at room-temp. for 20 min. The action is not stopped, but instead UV-abs is measured at a fixed time (20 min.) Due to autohydrolysis of the substrate the reaction is read at t = 0 min. too and t = 20 min. and the increase in Abs is calculated as the difference between the two readings. When a compound that inhibits HSL is present, it results in a relative decrease in UV-absorbance.

$$\% \text{Eff} (\% \text{Inhibition}) = (S - S_{0\text{Eff}}) / (S_{\text{maxEff}} - S_{0\text{Eff}}) \times 100$$

- Where S = signal in UV-abs., S<sub>0Eff</sub> = assaybuffer alone, S<sub>maxEff</sub> = Assaybuffer with the lipase inhibitor.

- 2898.2: This method is an enzyme assay based upon SPA (scintillation proximity assay) particles. The substrate, 1,3-(di-[<sup>3</sup>H]-stearin), 2-(PEG-Biotin)-glycerol, is marked with <sup>3</sup>H in both fatty acid moieties in the tri-glyceride. The third moiety of the tri-glyceride is a PEG linked Biotin. The substrate binds through Biotin to streptavidin in the SPA particles and the proximity between the radioactive tritium in the stearic acid moiety and the SPA particle results in emission of light from the SPA particles. The assay is an on-bead assay where HSL degrades the substrate, where after <sup>3</sup>H-stearin acid is released from the bead. The amount of light emitted is proportional to the amount of substrate bound to the receptor. When a compound that inhibits the activity of HSL is present it results in a decrease in degradation of the substrate and thus an increase in the amount of light emitted and a concomitant increase in %Eff.

$$\% \text{Eff } (\% \text{Inhibition}) = (S - S0\text{Eff}) / (S_{\text{maxEff}} - S0\text{Eff}) \times 100$$

Where S = signal in dpm., S0Eff = no inhibitor added, SmaxEff = with maximum concentration of inhibitor.

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## RESULTS

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With these methods the following results were obtained for the compounds of the examples.

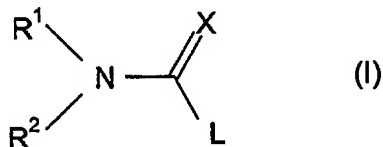
<b>Compound according to example #</b>	<b>Test 3190.1 HSL_FL % ACTIVITY All</b>	<b>Test 3180.2 HSL % ACTIVITY All</b>	<b>Test 2898.2 HSL-2 % Inhibition All</b>	<b>Test 2848.2 HSL % Inhibition All</b>
120		40		
122		14		
123		22		
121		24		
118		24		
119		10		
47	42			
46	43			
11	17			
87	48			
81	36			
48	15			
61	23			
6	49			
85	88			

90	24			
54	52			
62	88			
59	16			
24	30			
20	51			
92		62		
73	39			
109				15.9
106				23.8
108				37.2
114				42.4
126				33
110				18.8
111				36.2
107				59.9
105				26.8
104				19.8
127				58.7
128				33.8
103		2	101.4	
115		85	73.6	
113			18.3	
129				27
112			86	
116				23.5
124			75.1	
117		2		
130				30.1

131				21.6
132				19.6
133			15.8	
144	25			

## CLAIMS

1. Use of a compound of the general formula I



wherein R<sup>1</sup> is selected from hydrogen, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl and C<sub>3-10</sub>-cycloalkyl, each of which is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, oxo, halogen, amino, cyano and nitro; and

R<sup>2</sup> is selected from C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl, each of which is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, perhalomethyl and perhalomethoxy; and

wherein R<sup>2</sup> is optionally covalently bound to R<sup>1</sup> by an ether, thioether, C-C or C-N bond, to form a ring system with the N-atom to which R<sup>1</sup> and R<sup>2</sup> are bound; and

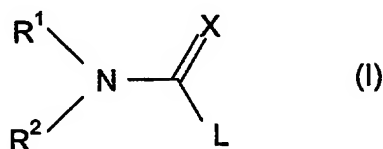
X is O or S; and

L is a group such that -C(=X)-L is a hydrolysable group; or

- 5 a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, or any tautomeric forms, stereoisomers, mixture of stereoisomers including a racemic mixture, or polymorphs

10 for inhibition of the lipolytic activity of hormone-sensitive lipase against triacylglycerols, diacylglycerols, cholesterol acyl esters or steroid acyl esters.

2. Use of a compound of the general formula I



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wherein R<sup>1</sup> is selected from hydrogen, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl and C<sub>3-10</sub>-cycloalkyl, each of which is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, oxo, halogen, amino, cyano and nitro; and

- 20 R<sup>2</sup> is selected from C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl, each of which is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo,
- 25
- 30

halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, perhalomethyl and perhalomethoxy; and

wherein R<sup>2</sup> is optionally covalently bound to R<sup>1</sup> by an ether, thioether, C-C or C-N bond, to form a ring system with the N-atom to which R<sup>1</sup> and R<sup>2</sup> are bound; and

X is O or S; and

L is a group such that -C(=X)-L is a hydrolysable group; or

a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, or any tautomeric forms, stereoisomers, mixture of stereoisomers including a racemic mixture, or polymorphs

for the preparation of a medicament for the treatment of any disorder where it is desirable to

modulate the plasma level of free fatty acids, glycerol, LDL-cholesterol, HDL-cholesterol, insulin and/or glucose; and/or

modulate intracellular triacylglycerol and cholesterol ester stores, intracellular level of fatty acids, fatty acid esters such as diacylglycerols, phosphatidic acids, long chain acyl-CoA's as well as citrate or malonyl-CoA; and/or

increase insulin sensitivity in adipose tissue, skeletal muscle, liver or pancreatic  $\beta$  cells; and/or

modulate insulin secretion from pancreatic  $\beta$  cells.

3. Use of a compound of the general formula I according to claim 1 for the preparation of a pharmaceutical medicament.



4. Use of a compound of the general formula (I) according to claim 1 for the preparation of a medicament for the treatment of insulin resistance, diabetes type 1, diabetes type 2, metabolic syndrome X, impaired glucose tolerance, hyperglycemia, dyslipidemia, obesity, abnormalities of lipoprotein metabolism and any combination thereof.

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5. The use according to any one of claims 1-4, wherein X is O.

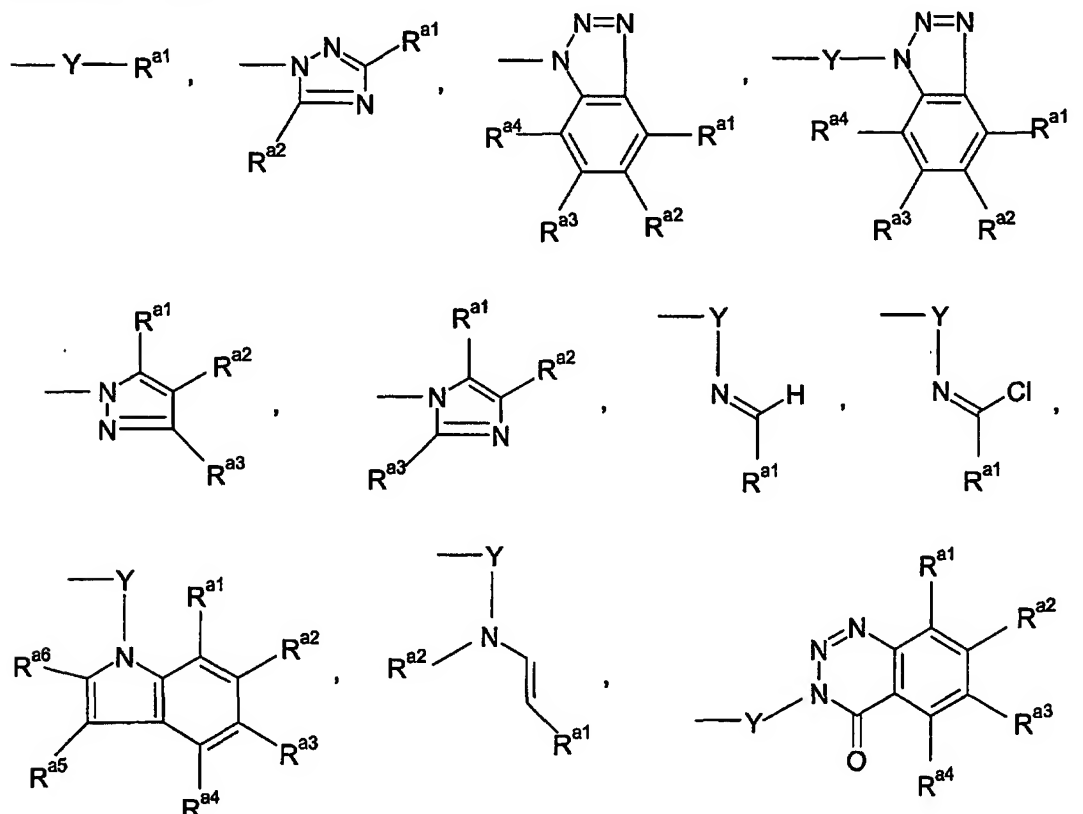
6. The use according to any one of claims 1-5, wherein the group L comprises an O, via which L is bound to the C in formula (I).

10

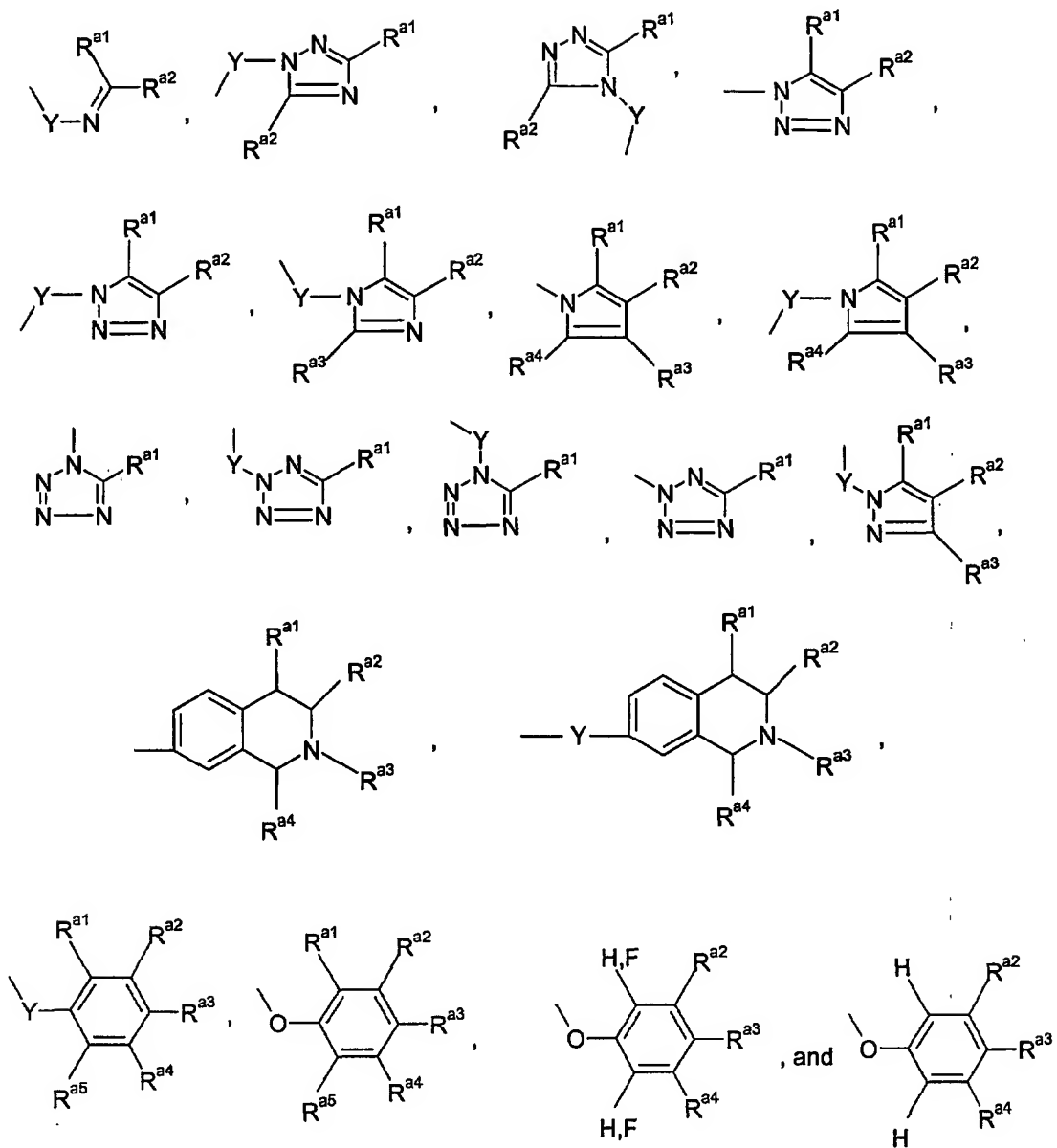
7. The use according to any one of claims 1-5, wherein the group L comprises a N, via which L is bound to the C in formula (I).

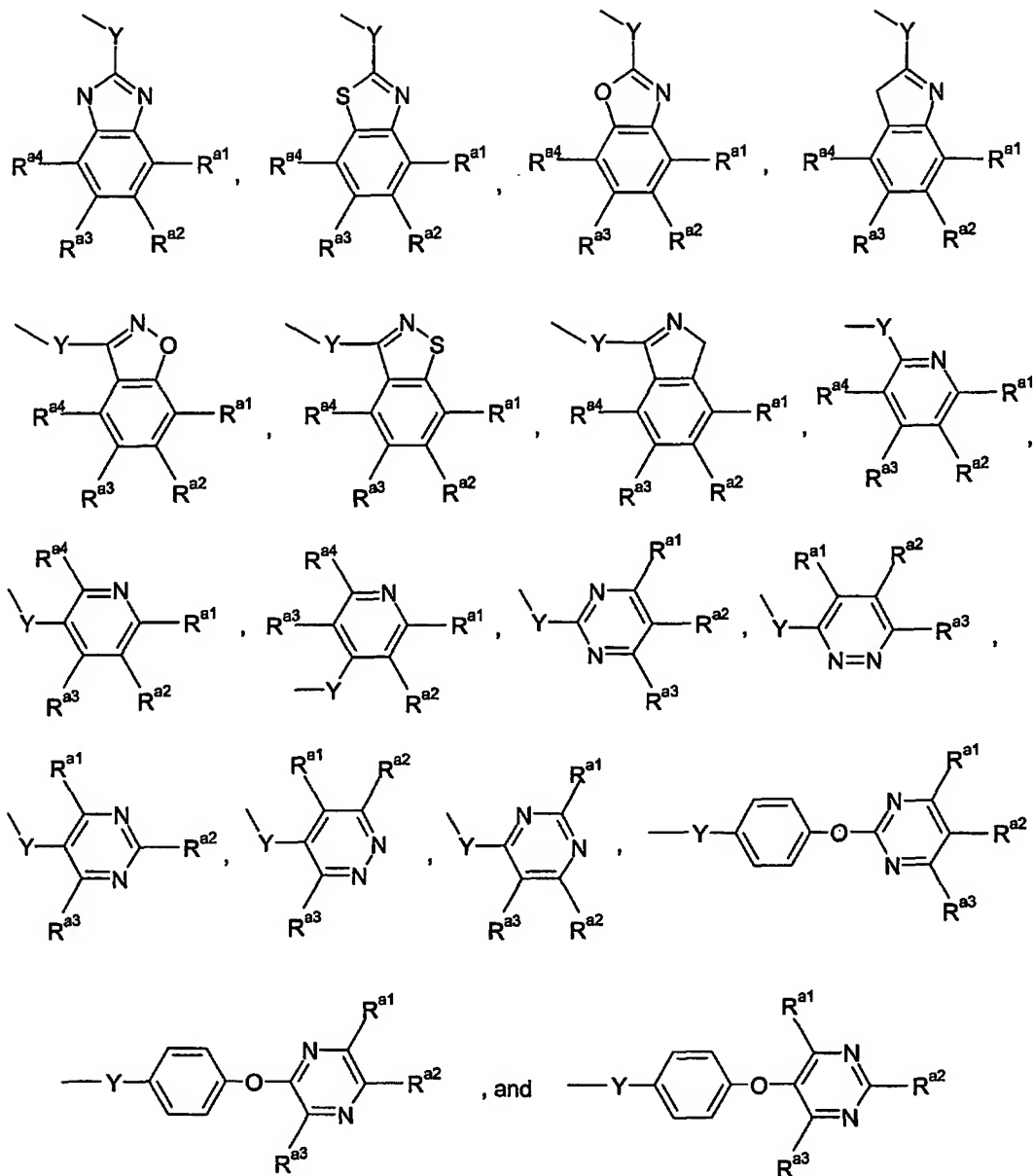
8. The use according to any one of claims 1-5, wherein the group L is selected from the group consisting of

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wherein Y is O or S; and

- 5  $R^{a1}$ ,  $R^{a2}$ ,  $R^{a3}$ ,  $R^{a4}$ ,  $R^{a5}$  and  $R^{a6}$  are independently selected from hydrogen, hydroxy, sulfanyl, sulfo, halogen, amino, cyano, nitro,  $C_{1-6}$ -alkyl,  $C_{2-6}$ -alkenyl, aryl, heteroaryl,  $C_{3-8}$ -heterocyclyl, or  $C_{3-10}$ -cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino,  $C_{1-6}$ -alkyl,  $C_{2-6}$ -alkenyl, aryl, heteroaryl,  $C_{3-8}$ -heterocyclyl and  $C_{3-10}$ -cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino,

- cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, perhalomethyl and perhalomethoxy.
9. The use according to claim 8, wherein at least one of R<sup>a1</sup>, R<sup>a2</sup>, R<sup>a3</sup>, R<sup>a4</sup>, R<sup>a5</sup> and R<sup>a6</sup> is F.
10. The use according to any one of claims 1-6, wherein the group L is an optionally substituted -O-phenyl, via which L is bound to the C in formula (I).
11. The use according to any one of claims 1-10, wherein R<sup>1</sup> and R<sup>2</sup> are covalently bound to each other so that the group R<sup>1</sup>-N-R<sup>2</sup> forms a piperazine, said piperazine being bound to the C in formula (I).
12. The use according to any one of claims 1-10, wherein R<sup>1</sup> and R<sup>2</sup> are covalently bound to each other so that the group R<sup>1</sup>-N-R<sup>2</sup> forms a piperidine, said piperidine being bound to the C in formula (I).
13. The use according to any one of claims 1-10, wherein R<sup>1</sup> is selected from the group consisting of C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl and C<sub>3-10</sub>-cycloalkyl, each of which is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, oxo, halogen, amino, cyano and nitro.
14. The use according to any one of claims 1-10, wherein R<sup>1</sup> is methyl.
15. The use according to any one of claims 1-10, wherein R<sup>2</sup> is phenyl.

16. The use according to any one of claims 1-10, wherein  $R^2$  is a heteroaryl.
17. The use according to any one of claims 1-10, wherein  $R^1$  is methyl and  $R^2$  is phenyl.
- 5 18. The use according to any one of claims 1-6, wherein the group L is an optionally substituted -O-phenyl via which L is bound to the C in formula (I), and  $R^1$  and  $R^2$  are covalently bound to each other so that the group  $R^1$ -N- $R^2$  forms a piperazine, said piperazine being bound to the C in formula (I).
- 10 19. The use according to any one of claims 1-6, wherein the group L is an optionally substituted -O-phenyl via which L is bound to the C in formula (I), and  $R^1$  and  $R^2$  are covalently bound to each other so that the group  $R^1$ -N- $R^2$  forms a piperidine, said piperidine being bound to the C in formula (I).
- 15 20. The use according to any one of claims 1-6, wherein the group L is an optionally substituted -O-phenyl via which L is bound to the C in formula (I), and  $R^1$  is methyl and  $R^2$  is phenyl.
- 20 21. The use according to any one of claims 1-20, wherein  $pK_a$  of the group L is between 4 and 12, between 6 and 12, between 7 and 12, between 8 and 12, preferably between 8.5 to 11.5, and most preferable between 9.0 to 11.0.
- 25 22. The use according to any one of claims 1-21, wherein administration of said compound is by the oral route.
23. The use according to any one of claims 1-21, wherein administration of said compound is by the nasal, transdermal, pulmonal, or parenteral route.
- 30 24. A method of treating any disorder where it is desirable to inhibit the lipolytic activity of hormone-sensitive lipase against triacylglycerols, diacylglycerols, cholesterol acyl esters or steroid acyl esters, wherein said method comprises the use according to any one of claims 1-23.

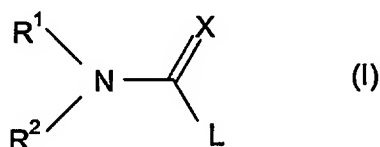
25. A method of treating any disorder where it is desirable to modulate the plasma level of free fatty acids or to modulate the handling, storage and oxidation of intracellular fatty acid and cholesterol, wherein said method comprises the use according to any one of claims 1-23.

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26. The method according to any one of claims 24-25, wherein said disorder is selected from the group consisting of insulin resistance, diabetes type 1, diabetes type 2, metabolic syndrome X, impaired glucose tolerance, hyperglycemia, dyslipidemia, obesity, abnormalities of lipoprotein metabolism and any combination thereof.

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27. A pharmaceutical composition comprising a compound of formula I



15 wherein  $\text{R}^1$  is selected from hydrogen,  $\text{C}_{1-6}$ -alkyl,  $\text{C}_{2-6}$ -alkenyl and  $\text{C}_{3-10}$ -cycloalkyl, each of which is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, oxo, halogen, amino, cyano and nitro; and

$\text{R}^2$  is selected from  $\text{C}_{1-6}$ -alkyl,  $\text{C}_{2-6}$ -alkenyl, aryl, heteroaryl,  $\text{C}_{3-8}$ -heterocyclyl and  $\text{C}_{3-10}$ -cycloalkyl, each of which is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro,  $\text{C}_{1-6}$ -alkyl,  $\text{C}_{2-6}$ -alkenyl, aryl, heteroaryl,  $\text{C}_{3-8}$ -heterocyclyl and  $\text{C}_{3-10}$ -cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino,  $\text{C}_{1-6}$ -alkyl,  $\text{C}_{2-6}$ -alkenyl, aryl, heteroaryl,  $\text{C}_{3-8}$ -heterocyclyl and  $\text{C}_{3-10}$ -cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro,  $\text{C}_{1-6}$ -alkyl,  $\text{C}_{2-6}$ -alkenyl, aryl, heteroaryl,  $\text{C}_{3-8}$ -heterocyclyl and  $\text{C}_{3-10}$ -cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino,  $\text{C}_{1-6}$ -alkyl,  $\text{C}_{2-6}$ -alkenyl, aryl, heteroaryl,  $\text{C}_{3-8}$ -heterocyclyl and  $\text{C}_{3-10}$ -cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro,  $\text{C}_{1-6}$ -alkyl,  $\text{C}_{2-6}$ -alkenyl, aryl, heteroaryl,  $\text{C}_{3-8}$ -heterocyclyl and  $\text{C}_{3-10}$ -cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino,  $\text{C}_{1-6}$ -alkyl,  $\text{C}_{2-6}$ -alkenyl, aryl, heteroaryl,  $\text{C}_{3-8}$ -heterocyclyl and  $\text{C}_{3-10}$ -cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro,  $\text{C}_{1-6}$ -alkyl,  $\text{C}_{2-6}$ -alkenyl, aryl, heteroaryl,  $\text{C}_{3-8}$ -heterocyclyl and  $\text{C}_{3-10}$ -cycloalkyl.

<sub>10</sub>-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, perhalomethyl and perhalomethoxy; and

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wherein R<sup>2</sup> is optionally covalently bound to R<sup>1</sup> by an ether, thioether, C-C or C-N bond, to form a ring system with the N-atom to which R<sup>1</sup> and R<sup>2</sup> are bound; and

X is O or S; and

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L is a group such that -C(=X)-L is a hydrolysable group; or

a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, or any tautomeric forms, stereoisomers, mixture of stereoisomers including a racemic mixture, or polymorphs

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28. The pharmaceutical composition according to claim 27, wherein X is O.

29. The pharmaceutical composition according to any one of claims 27-28, wherein the group L comprises an O, via which L is bound to the C in formula (I).

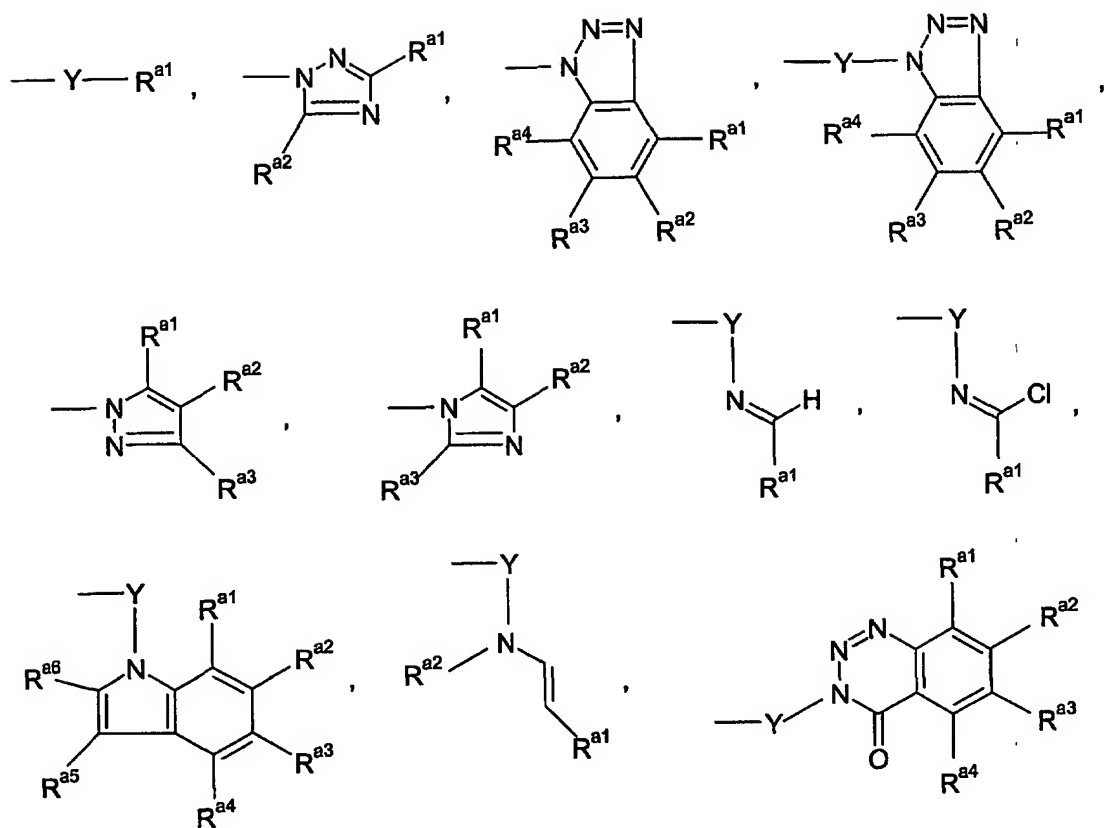
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30. The pharmaceutical composition according to any one of claims 27-28, wherein the group L comprises a N, via which L is bound to the C in formula (I).

31. The pharmaceutical composition according to any one of claims 27-29, wherein the group L is selected from the group consisting of

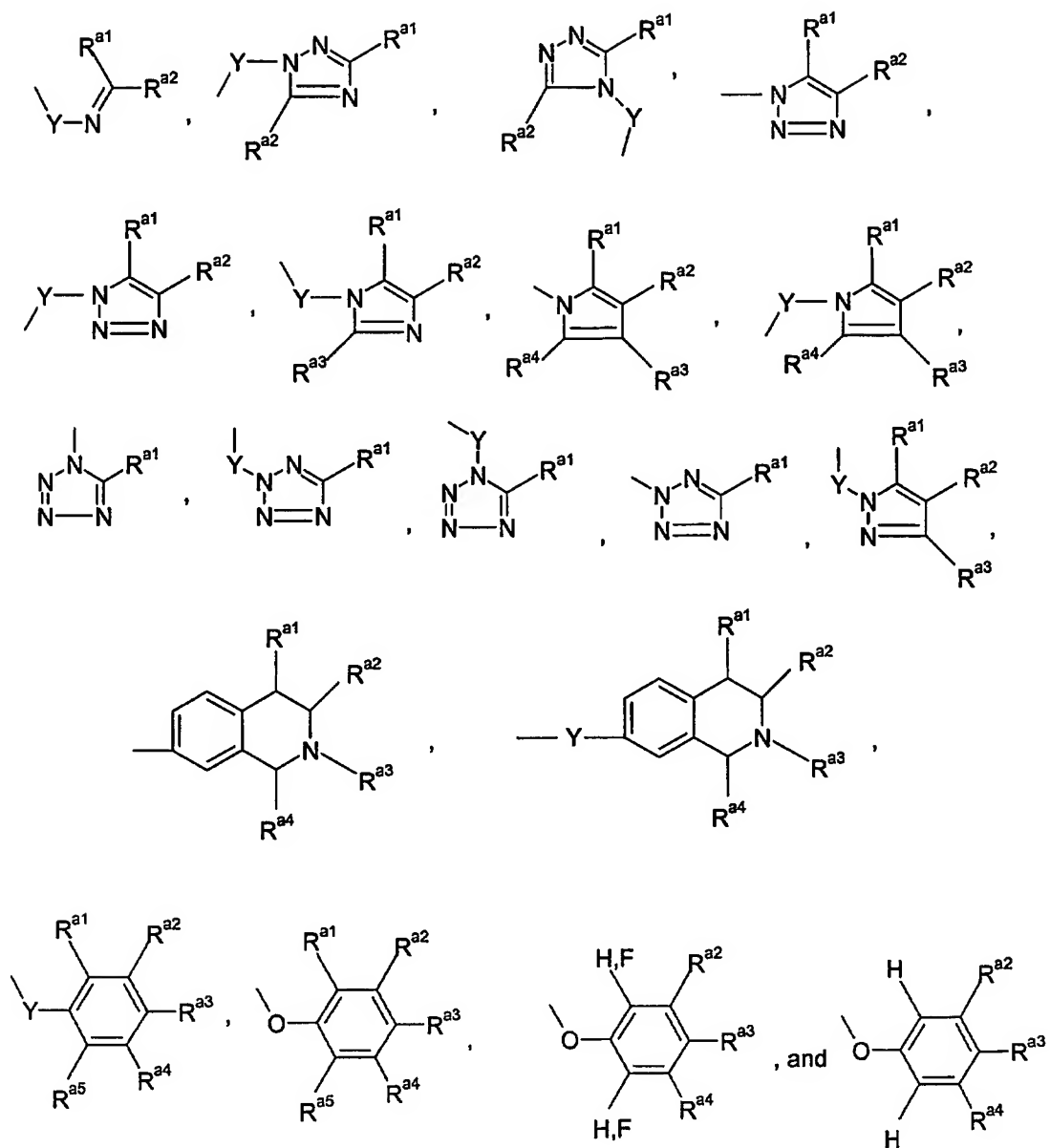
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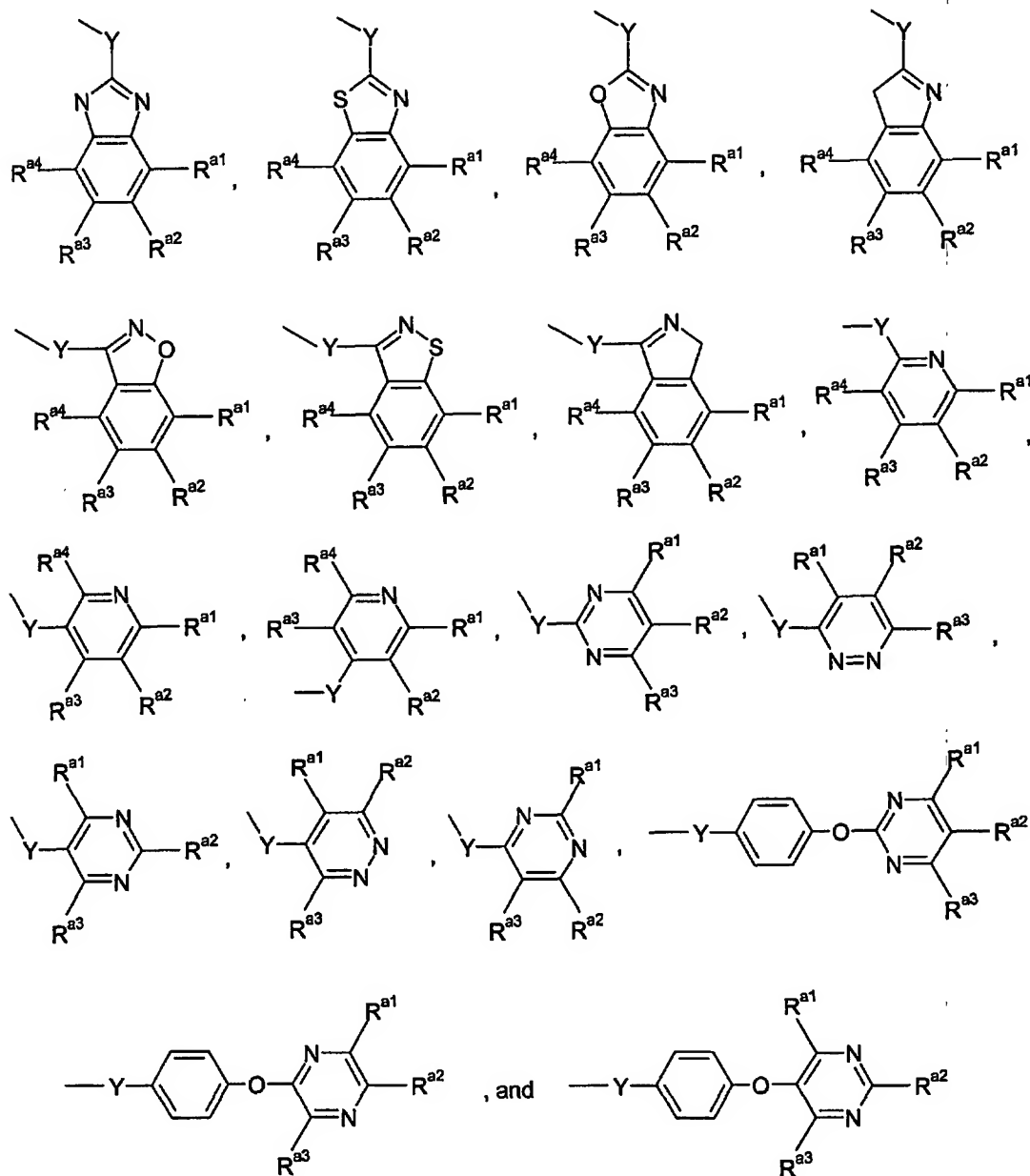
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wherein  $Y$  is O or S; and

- 5  $R^{a1}$ ,  $R^{a2}$ ,  $R^{a3}$ ,  $R^{a4}$ ,  $R^{a5}$  and  $R^{a6}$  are independently selected from hydrogen, hydroxy, sulfanyl, sulfo, halogen, amino, cyano, nitro,  $C_{1-6}$ -alkyl,  $C_{2-6}$ -alkenyl, aryl, heteroaryl,  $C_{3-8}$ -heterocyclyl, or  $C_{3-10}$ -cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino,  $C_{1-6}$ -alkyl,  $C_{2-6}$ -alkenyl, aryl, heteroaryl,  $C_{3-8}$ -heterocyclyl and  $C_{3-10}$ -cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino,

- cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfo, amino, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, aryl, heteroaryl, C<sub>3-8</sub>-heterocyclyl and C<sub>3-10</sub>-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfo, oxo, halogen, amino, cyano, nitro, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, perhalomethyl and perhalomethoxy.
32. The pharmaceutical composition according to claim 31, wherein at least one of R<sup>a1</sup>, R<sup>a2</sup>, R<sup>a3</sup>, R<sup>a4</sup>, R<sup>a5</sup> and R<sup>a6</sup> is F.
33. The pharmaceutical composition according to any one of claims 27-29, wherein the group L is an optionally substituted -O-phenyl, via which L is bound to the C in formula (I).
34. The pharmaceutical composition according to any one of claims 27-33, wherein R<sup>1</sup> and R<sup>2</sup> are covalently bound to each other so that the group R<sup>1</sup>-N-R<sup>2</sup> forms a piperazine, said piperazine being bound to the C in formula (I).
35. The pharmaceutical composition according to any one of claims 27-33, wherein R<sup>1</sup> and R<sup>2</sup> are covalently bound to each other so that the group R<sup>1</sup>-N-R<sup>2</sup> forms a piperidine, said piperidine being bound to the C in formula (I).
36. The pharmaceutical composition according to any one of claims 27-33, wherein R<sup>1</sup> is selected from the group consisting of C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl and C<sub>3-10</sub>-cycloalkyl, each of which is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, oxo, halogen, amino, cyano and nitro.
37. The pharmaceutical composition according to any one of claims 27-33, wherein R<sup>1</sup> is methyl.

38. The pharmaceutical composition according to any one of claims 27-33, wherein R<sup>2</sup> is phenyl.

5 39. The pharmaceutical composition according to any one of claims 27-33, wherein R<sup>2</sup> is a heteroaryl.

40. The pharmaceutical composition according to any one of claims 27-33, wherein R<sup>1</sup> is methyl and R<sup>2</sup> is phenyl.

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41. The pharmaceutical composition according to any one of claims 27-29, wherein the group L is an optionally substituted -O-phenyl via which L is bound to the C in formula (I), and R<sup>1</sup> and R<sup>2</sup> are covalently bound to each other so that the group R<sup>1</sup>-N-R<sup>2</sup> forms a piperazine, said piperazine being bound to the C in formula (I).

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42. The pharmaceutical composition according to any one of claims 27-29, wherein the group L is an optionally substituted -O-phenyl via which L is bound to the C in formula (I), and R<sup>1</sup> and R<sup>2</sup> are covalently bound to each other so that the group R<sup>1</sup>-N-R<sup>2</sup> forms a piperidine, said piperidine being bound to the C in formula (I).

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43. The pharmaceutical composition according to any one of claims 27-29, wherein the group L is an optionally substituted -O-phenyl via which L is bound to the C in formula (I), and R<sup>1</sup> is methyl and R<sup>2</sup> is phenyl.

25 44. The pharmaceutical composition according to any one of claims 27-43, wherein pK<sub>a</sub> of the group L is between 4 and 12, between 6 and 12, between 7 and 12, between 8 and 12, preferably between 8.5 to 11.5, and most preferable between 9.0 to 11.0.

30 45. The pharmaceutical composition according to any one of claims 27-44, which is for oral administration.

46. The pharmaceutical composition according to any one of claims 27-44, which is for administration by the nasal, transdermal, pulmonal, or parenteral route.

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(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
26 June 2003 (26.06.2003)

PCT

(10) International Publication Number  
**WO 2003/051842 A3**

(51) International Patent Classification<sup>7</sup>: **A61K 31/325**,  
31/4196, 31/4192, 31/415, 31/352, 31/4035, 31/40,  
31/404, 31/423, 31/42, 31/428, 31/44, 31/495, 31/505,  
31/41

DK-2880 Bagsværd (DK). JACOBSEN, Poul, Morænevej  
2A, DK-3500 Slangerup (DK).

(21) International Application Number:  
PCT/DK2002/000853

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,  
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE,  
SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC,  
VN, YU, ZA, ZM, ZW.

(22) International Filing Date:  
13 December 2002 (13.12.2002)

(25) Filing Language: English

(84) Designated States (*regional*): ARIPO patent (GI, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,  
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK,  
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,  
GW, ML, MR, NE, SN, TD, TG).

(26) Publication Language: English

(30) Priority Data:  
PA 2001 01879 14 December 2001 (14.12.2001) DK  
PA 2002 00645 30 April 2002 (30.04.2002) DK  
PA 2002 01000 27 June 2002 (27.06.2002) DK  
PA 2002 01562 11 October 2002 (11.10.2002) DK

**Published:**

- with international search report
- before the expiration of the time limit for amending the  
claims and to be republished in the event of receipt of  
amendments

(71) Applicant: NOVO NORDISK A/S [DK/DK]; Novo Allé,  
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(88) Date of publication of the international search report:  
3 June 2004

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CORNELIS DE JONG, Johannes; Møllemarken 16, 1th,

For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.



WO 2003/051842 A3

(54) Title: COMPOSITIONS DECREASING ACTIVITY OF HORMONE-SENSITIVE LIPASE

(57) Abstract: Carbamates and related compounds of formula R1R2NCO-Y or R1R2NCS-Y wherein R1 and R2 may form a ring, are inhibitors of hormone sensitive lipase and are useful for the treatment of any disorder where it is desirable to modulate the plasma level of free fatty acids, glycerol, LDL-cholesterol, HDL-cholesterol, insulin and/or glucose; and or modulate intracellular triacylglycerol and cholesterol stores, intracellular level of fatty acids, fatty acid esters such as diacylglycerols, phosphatidic acids, long chain acyl-CoA's as well as citrate or malonyl-CoA; and or increase insulin sensitivity; and or modulate insulin secretion from pancreatic beta cells. More particularly said disorders are selected from the group consisting of insulin resistance, diabetes type 1, hyperglycemia, dislipidemia, obesity, abnormalities of lipoprotein metabolism and any combinations thereof.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 02/00853

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/325 A61K31/4196 A61K31/4192 A61K31/415 A61K31/352  
A61K31/4035 A61K31/40 A61K31/404 A61K31/423 A61K31/42  
A61K31/428 A61K31/44 A61K31/495 A61K31/505 A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS, EMBASE, BEILSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/69810 A (NOVO NORDISK AS ; AGOURON PHARMA (US)) 23 November 2000 (2000-11-23)  abstract; examples 398-421 -----	1-6, 8-10, 13, 20-29, 31, 33, 36, 44-46
X	WO 02/20483 A (HOFFMANN LA ROCHE) 14 March 2002 (2002-03-14) abstract examples 1.3, 1.11-1.14, 3.5, 3.6, 3.11, 3.12, 4.5-4.8, 4. 13, 4.14, claims 24, 25, 31, 33, 35; examples 4.19-4.22, 6, 7 ----- -/-	1

☒ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search

3 December 2003

Date of mailing of the international search report

31 03. 2004

Name and mailing address of the ISA

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 02/00853

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 02/06189 A (HOFFMANN LA ROCHE) 24 January 2002 (2002-01-24)</p> <p>abstract page 9, line 26 - page 10, line 10 page 17, lines 13-19 page 19, lines 19-26 page 21, line 27 - page 22, line 2 page 23, line 3 - page 24, line 4 page 35, line 26 - page 37, line 11; examples 4.1-4.17 claims 1-20,24; examples 9.1-9.4</p>	<p>1-6, 8-10,13, 14, 21-29, 31-33, 36,37, 39,44-46</p>
X	<p>WO 99/62870 A (ANDERSSON KJELL ;ASTRA AB (SE); LINDSTEDT ALSTERMARK EVA LOTTE (SE) 9 December 1999 (1999-12-09)</p> <p>abstract page 20, line 25 - page 21, line 15</p>	<p>1-6,8,9, 21-29, 31,44-46</p>
X	<p>WO 02/38153 A (BESENCON OLIVIER ;OLSSON ROLF (SE); BIOVITRUM AB (SE); OEHMAN JOHA) 16 May 2002 (2002-05-16)</p> <p>abstract page 5, lines 1-26 claims 1-9; examples 6-13,17-26,28-39; tables 2,3</p>	<p>1-6, 8-10, 21-29, 31-33, 44-46</p>
X	<p>WO 01/021584 A (GENENTECH INC ;JACKSON DAVID Y (US); SAILES FREDERICK C (US); SUTH) 29 March 2001 (2001-03-29)</p> <p>abstract page 19, line 23 - page 20, line 2; claims 1-24; examples 1-9,11-42,44-57,111-128; tables 2,3</p>	<p>1-6,8, 10, 13-16, 21-29, 31,33, 36-39, 44-46</p>
X	<p>WO 00/63208 A (BOEHRINGER INGELHEIM INT ;NOVO NORDISK AS (DK)) 26 October 2000 (2000-10-26)</p> <p>abstract page 23, line 22 - page 28, line 4 page 55, line 18 - page 56, line 26; claims 1-47</p>	<p>1</p>

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 02/00853

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE WPI  Section Ch, Week 199709  Derwent Publications Ltd., London, GB;  Class B03, AN 1997-100136  XP002230558  &amp; WO 97/01533 A (GREEN CROSS CORP)  16 January 1997 (1997-01-16)  abstract</p>	<p>1-6,8,  13,  21-29,  31,36,  44-46</p>
X	<p>EP 1 201 649 A (PFIZER PROD INC)  2 May 2002 (2002-05-02)  abstract  page 17, lines 31-51  page 24, line 37 - page 25, line 40;  claims 1-13; examples 1-87</p>	<p>1</p>
X	<p>US 5 837 727 A (BAUER CARL-AXEL WILHELM  EDVARD ET AL)  17 November 1998 (1998-11-17)</p> <p>abstract; claims 1-7</p>	<p>1-6,8,  10,13,  14,  20-29,  31,33,  36,37,  44-46</p>
X	<p>US 5 463 062 A (HEMMERLE HORST ET AL)  31 October 1995 (1995-10-31)</p> <p>abstract  column 5, lines 26-47; claims 1-11;  examples 102,103</p>	<p>1-6,8,  13,  21-29,  31,44-46</p>
X	<p>WO 98/53814 A (HAGMANN WILLIAM K ;MUMFORD  RICHARD A (US); KEVIN NANCY J (US); MAC)  3 December 1998 (1998-12-03)</p> <p>abstract  page 20, line 21 - page 21, line 10;  claims 17-20; examples 272,319-324</p>	<p>1-6,8,  10,13,  14,  20-29,  31,33,  36,37,  44-46</p>

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 02/00853

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 00/54759 A (TULARIK INC) 21 September 2000 (2000-09-21)</p> <p>abstract page 2, lines 13-29 page 3, line 25 - page 4, line 22 page 13, lines 1-7; claims 1,9,27,28,40-45; examples 7-7.6 -----</p>	<p>1-6,8, 10,13, 14, 21-29, 31,33, 36,37, 44-46</p>
X	<p>WO 01/021602 A (DEVASTHALE PRATIK ;SQUIBB BRISTOL MYERS CO (US); CHEN SEAN (US); J) 29 March 2001 (2001-03-29)</p> <p>page 1, line 1 - page 16, line 27 -----</p>	<p>1-6,8, 10,13, 20-29, 31,33, 44-46</p>
X,P	<p>WO 02/12210 A (BERNARDON JEAN MICHEL ;CLARY LAURENCE (FR); GALDERMA RES &amp; DEV (FR) 14 February 2002 (2002-02-14)</p> <p>abstract; examples 11,19-21,27,61,70,73,74 page 8, lines 37,38 page 9, lines 4-6,12-14 page 14, line 6 - page 15, line 19 -----</p>	<p>1-6,8, 10,13, 15, 21-29, 31,33, 36,38, 44-46</p>
E	<p>WO 03/040114 A (DEVASTHALE PRATIK ;SQUIBB BRISTOL MYERS CO (US); JEON YOON T (US)) 15 May 2003 (2003-05-15)</p> <p>abstract page 6, line 1 - page 7, line 17 -----</p>	<p>1-6,8, 10,13, 21-29, 31,33, 36,44-46</p>
X	<p>WO 92/07838 A (BEECHAM GROUP PLC) 14 May 1992 (1992-05-14)</p> <p>abstract page 1, line 15 - page 3, line 7; examples 1-5,11,12 -----</p>	<p>1-6,8, 10, 13-15, 21-29, 31,33, 36-38, 44-46</p>

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 02/00853

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/087843 A (CORNELIS DE JONG JOHANNES ;JACOBSEN POUL (DK); NOVO NORDISK AS (DK) 22 November 2001 (2001-11-22)  abstract page 3, line 1 - page 18, line 9 page 25, line 32 - page 26, line 9; claims 1-22; examples 1-50; table 1 -----	1-6, 8-10, 21-29, 31-33, 39,44-46
X	US 5 869 484 A (MARCHESINI DONATA ET AL) 9 February 1999 (1999-02-09)  abstract; examples 1-28 -----	27-29, 31,33, 36,44-46
X	WO 01/047923 A (ASTRAZENECA AB ;BARE THOMAS MICHAEL (US); BROWN DEAN GORDON (US);) 5 July 2001 (2001-07-05)  abstract page 20, lines 22-25; table 1 -----	27-29, 31,33, 36-38, 40,43-46
X	US 4 643 991 A (TSUJI KIYOSHI ET AL) 17 February 1987 (1987-02-17)  abstract; examples 6-11,16,17,19-21,23-31,33-38,40-42,44-46,4 8-50 examples 52-63,65-67,69-83,85-87,93,97-99 -----	27-29, 31-33, 36,37, 44-46
X	WO 95/29155 A (PHARMACIA AB ;FEX TOMAS (SE); STAMVIK ANDERS (SE); CARLSSON JAN IN) 2 November 1995 (1995-11-02)  abstract page 14, lines 21-25; examples 4,5 page 27, line 31 - page 28, line 20 page 57, lines 24-30 page 59, lines 14-16,21-23 page 61, lines 1-3 page 66, lines 19-25 page 68, lines 1-3 page 71, lines 1-7 page 72, lines 19-21,26-29 page 74, lines 5-7; claims 10-12 -----	27-29, 31,33, 36,37, 44-46
X	BE 665 273 A (FARBENFAB BAYER AG) 1 October 1965 (1965-10-01)  page 6, paragraph 3 - page 12, paragraph 4 -----	27-29, 31,33, 36-38, 40,43-46
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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/DK 02/00853

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	<p>WO 02/42257 A (CASTRO PALOMINO JULIO ;EBBINGHAUS KINTSCHER ULRICH (DE); SCHUHMACH) 30 May 2002 (2002-05-30)</p> <p>abstract page 57, line 20 - page 58 page 82; examples XXXVI,XV examples 148-151,157-176,204,205,231,232,283,284</p>	<p>27-29, 31,33, 36,38, 44-46</p>
X	<p>EP 0 587 311 A (SANKYO CO) 16 March 1994 (1994-03-16) examples 1-12,15,16,19,22,24,26,28,29,34,36,37,42,4 9,51-53,57,59,65,66,68,70,71,73,74,76,77,8 8-94, abstract; claims 19,20</p>	<p>1</p>
X	<p>SCHMIDT F ET AL: "Glucuronide prodrugs of hydroxy compounds for antibody directed enzyme prodrug therapy (adept): a phenol nitrogen mustard carbamate" BIOORGANIC &amp; MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 7, no. 8, 22 April 1997 (1997-04-22), pages 1071-1076, XP004136187 ISSN: 0960-894X abstract</p>	<p>1</p>
A	<p>WO 92/06075 A (WELLCOME FOUND) 16 April 1992 (1992-04-16) abstract; example 15</p>	<p>1</p>

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/DK 02/00853

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 1,4-26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
  
1-6,8-10,13-17,20-29,31-33,36-40,44-46 (all partially) 43

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-6,8-10,13-17,20-29,31-33,36-40,44-46 (all partially)  
43

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is not covalently bound to R2 and wherein L is selected from the group consisting of the first, 27th, 28th, 29th, 30th, 46th 47th and 48th group of claim 8 (-Y-Ra1, Ra1 in -Y-Ra1 having any value given in claim 8 (and in particular substituted 0-phenyl) except heteroaryl and heterocyclyl).

---

2. claims: 1-9,13-17,20-29,31,32,36-40,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is not covalently bound to R2 and wherein L is selected from the group consisting of the group 2, 13 and 14 of claim 8 (1,2,4-triazolyl group).

---

3. claims: 1-9,13-17,20-29,31,32,36-40,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is not covalently bound to R2 and wherein L is selected from the group consisting of the 3rd and 4th group of claim 8 (1,2,3-benzotriazolyl group).

---

4. claims: 1-9,13-17,20-29,31,32,36-40,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is not covalently bound to R2 and wherein L is selected from the group consisting of the group 5 or 24 of claim 8 (pyrazolyl group).

---

5. claims: 1-9,13-17,20-29,31-32,36-40,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is not covalently bound to R2 and wherein L is selected from the group consisting of the group 6 or 17 of claim 8 (imidazolyl group).

---

6. claims: 1-9,13-17,20-29,31,32,36-40,44-46 (all partially)

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is not covalently bound to R2 and wherein L is selected from the group consisting of the group 7, 8, 10 or 12 of claim 8 (Y-N=CRa1-H, Y-N=CRa1-Cl, Y-NCRa2CH=CHRa1, Y-N=CRa1Ra2).

---

7. claims: 1-6,8,9,13-17,20-29,31,32,36-40,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is not covalently bound to R2 and wherein L is selected from the group consisting of the group 9 of claim 8 (indol-1-yl group).

---

8. claims: 1-6,8,9,13-17,20-29,31,32,36-40,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is not covalently bound to R2 and wherein L is selected from the group consisting of the group 11 of claim 8 (3H-benzo(d)-1,2,3-triazin-4-one-3-yl group).

---

9. claims: 1-9,13-17,20-29,31,32,36-40,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is not covalently bound to R2 and wherein L is selected from the group consisting of the group 15 and 16 of claim 8 (1,2,3-triazolyl group).

---

10. claims: 1-9,13-17,20-29,31,32,36-40,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is not covalently bound to R2 and wherein L is selected from the group consisting of the group 18 and 19 of claim 8 (pyrrolyl group).

---

11. claims: 1-9,13-17,20-29,31,32,36-40,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is not covalently bound to R2 and wherein L is selected from the group consisting of the group 20, 21, 22, 23 of claim 8 (tetrazolyl group).

---

12. claims: 1-9,13-17,20-29,31,32,36-40,44-46 (all partially)

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is not covalently bound to R2 and wherein L is selected from the group consisting of the group 25, 26 of claim 8 (tetrahydro-1,2,3,4-isoquinolin-7-yl)(benzimidazol-2-yl, benzothiazol-2-yl-, benzoxazol-2-yl, 3H-indol-2-yl group).

---

13. claims: 1-9,13-17,20-29,31,32,36-40,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is not covalently bound to R2 and wherein L is selected from the group consisting of the group 31-34 of claim 8 (benzimidazol-2-yl, benzothiazol-2-yl-, benzoxazol-2-yl, 3H-indol-2-yl group).

---

14. claims: 1-9,13-17,20-29,31,32,36-40,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is not covalently bound to R2 and wherein L is selected from the group consisting of the group 35-37 of claim 8 (benzisoxazol-1-yl, benzisothiazol-1-yl, 3H-isoindol-1-yl group).

---

15. claims: 1-6,8,9,13-17,20-29,31,32,36-40,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is not covalently bound to R2 and wherein L is selected from the group consisting of the group 38, 39 or 40 of claim 8 (pyridinyl group) and the benzocondensed derivatives thereof like quinolin-2-yl of e.g example 244.

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16. claims: 1-6,8,9,13-17,20-29,31,32,36-40,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is not covalently bound to R2 and wherein L is selected from the group consisting of the group 41, 43, 45 of claim 8 (pyrimidin-2-yl, pyrimidin-3-yl or pyrimidin-4-yl).

---

17. claims: 1-6,8,9,13-17,20-29,31,32,36-40,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is not covalently bound to R2 and wherein L is selected from the group 42 and 44 of claim 8 (pyridazin-yl group).

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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18. claims: 1-6,8,9,13-17,20-29,31-,32,36-40,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is not covalently bound to R2 and wherein L is heteroaryl or heterocyclyl not provided for in inventions 2-17, e.g. chromenyl as of examples 12, 40-49.

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19. claims: 1-6,8-10,12,13,19,21-28,31-33,35,36,44-46 (all partially) 42

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by an ether, thioether or C-C bond to form a N-containing ring system, (e.g. morpholine, thiomorpholine, piperidine) and wherein L is selected from the group consisting of the first, 27th, 28th, 29th, 30th, 46th 47th and 48th group of claim 8 (-Y-Ra1, Ra1 in -Y-Ra1 having any value given in claim 8 (and in particular substituted O-phenyl) except heteroaryl and heterocyclyl).

---

20. claims: 1-9,12,13,19,21-32,35,36,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by an ether, thioether or C-C bond to form a N-containing ring system, (e.g. morpholine, thiomorpholine, piperidine) and wherein L is selected from the group consisting of the group 2, 13 and 14 of claim 8 (1,2,4-triazolyl group).

---

21. claims: 1-9,12,13,19,21-32,35,36,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by an ether, thioether or C-C bond to form a N-containing ring system, (e.g. morpholine, thiomorpholine, piperidine) and wherein L is selected from the group consisting of the 3rd and 4th group of claim 8 (1,2,3-benzotriazolyl group).

---

22. claims: 1-9,12,13,19,21-32,35,36,44-46 (all partially)



## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by an ether, thioether or C-C bond to form a N-containing ring system, (e.g. morpholine, thiomorpholine, piperidine) and wherein L is selected from the group consisting of the group 5 or 24 of claim 8 (pyrazolyl group).

---

23. claims: 1-9,12,13,19,21-32,35,36,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by an ether, thioether or C-C bond to form a N-containing ring system, (e.g. morpholine, thiomorpholine, piperidine) and wherein L is selected from the group consisting of the group 6 or 17 of claim 8 (imidazolyl group).

---

24. claims: 1-9,12,13,19,21-32,35,36,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by an ether, thioether or C-C bond to form a N-containing ring system, (e.g. morpholine, thiomorpholine, piperidine) and wherein L is selected from the group consisting of the group 7, 8, 10 or 12 of claim 8 (Y-N=CRa1-H, Y-N=CRa1-Cl, Y-NCRa2CH=CHRa1, Y-N=CRa1Ra2).

---

25. claims: 1-6,8,9,12,13,19,21-28,30-32,35,36,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by an ether, thioether or C-C bond to form a N-containing ring system, (e.g. morpholine, thiomorpholine, piperidine) and wherein L is selected from the group consisting of the group 9 of claim 8 (indol-1-yl group).

---

26. claims: 1-6,8,9,12,13,19,21-28,30-32,35,36,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by an ether, thioether or C-C bond to form a N-containing ring system, (e.g. morpholine, thiomorpholine, piperidine) and wherein L is selected from the group consisting of the group 11 of claim 8 (3H-benzo(d)-1,2,3-triazin-4-one-3-yl group).

---

27. claims: 1-9,12,13,19,21-32,35,36,44-46 (all partially)

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by an ether, thioether or C-C bond to form a N-containing ring system, (e.g. morpholine, thiomorpholine, piperidine) and wherein L is selected from the group consisting of the group 15 and 16 of claim 8 (1,2,3-triazolyl group).

---

28. claims: 1-9,12,13,19,21-32,35,36,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by an ether, thioether or C-C bond to form a N-containing ring system, (e.g. morpholine, thiomorpholine, piperidine) and wherein L is selected from the group consisting of the group 18 and 19 of claim 8 (pyrrolyl group).

---

29. claims: 1-9,12,13,19,21-32,35,36,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by an ether, thioether or C-C bond to form a N-containing ring system, (e.g. morpholine, thiomorpholine, piperidine) and wherein L is selected from the group consisting of the group 20, 21, 22, 23 of claim 8 (tetrazolyl group).

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30. claims: 1-9,12,13,19,21-32,35,36,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by an ether, thioether or C-C bond to form a N-containing ring system, (e.g. morpholine, thiomorpholine, piperidine) and wherein L is selected from the group consisting of the group 25, 26 of claim 8 (tetrahydro-1,2,3,4-isoquinolin-7-yl)(benzimidazol-2-yl, benzothiazol-2-yl-, benzoxazol-2-yl, 3H-indol-2-yl group).

---

31. claims: 1-6,8,9,12,13,19,21-28,30-32,35,36,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by an ether, thioether or C-C bond to form a N-containing ring system, (e.g. morpholine, thiomorpholine, piperidine) and wherein L is selected from the group consisting of the group 31-34 of claim 8 (benzimidazol-2-yl, benzothiazol-2-yl-, benzoxazol-2-yl, 3H-indol-2-yl group).

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# INTERNATIONAL SEARCH REPORT

International Application No. **DP02/00853** /

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

32. claims: 1-9,12,13,19,21-32,35,36,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by an ether, thioether or C-C bond to form a N-containing ring system, (e.g. morpholine, thiomorpholine, piperidine) and wherein L is selected from the group consisting of the group 35-37 of claim 8 (benzisoaxazol-1-yl, benzisothiazol-1-yl, 3H-isoindol-1-yl group).

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33. claims: 1-6,8,9,12,13,19,21-28,30-32,35,36,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by an ether, thioether or C-C bond to form a N-containing ring system, (e.g. morpholine, thiomorpholine, piperidine) and wherein L is selected from the group consisting of the group 38, 39 or 40 of claim 8 (pyridinyl group) and the benzocondensed derivatives thereof.

---

34. claims: 1-6,8,9,12,13,19,21-28,30-32,35,36,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by an ether, thioether or C-C bond to form a N-containing ring system, (e.g. morpholine, thiomorpholine, piperidine) and wherein L is selected from the group consisting of the group 41, 43, 45 of claim 8 (pyrimidin-2-yl, pyrimidin-3-yl or pyrimidin-4-yl).

---

35. claims: 1-6,8,9,12,13,19,21-28,30-32,35,36,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by an ether, thioether or C-C bond to form a N-containing ring system, (e.g. morpholine, thiomorpholine, piperidine) and wherein L is selected from the group 42 and 44 of claim 8 (pyridazin-yl group).

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36. claims: 1-6,8,9,12,13,19,21-28,30-32,35,36,44-46 (all partially)

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by an ether, thioether or C-C bond to form a N-containing ring system, (e.g. morpholine, thiomorpholine, piperidine) and wherein L is heteroaryl or heterocyclyl not provided for in inventions 20-35.

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37. claims: 1-6,8-11,18,20-28,31-34,45,46 (all partially) 41

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by a C-N bond to form a N-containing ring system, (e.g. piperazine, 1,4-diazepane, 2,5-diazabicyclo[2.2.1]heptane) and wherein L is selected from the group consisting of the first, 27th, 28th, 29th, 30th, 46th 47th and 48th group of claim 8 (-Y-Ral, Ral in -Y-Ral having any value given in claim 8 (and in particular substituted O-phenyl) except heteroaryl and heterocyclyl.

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38. claims: 1-9,11,18,21-32,34,36,39,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by a C-N bond to form a N-containing ring system, (e.g. piperazine, 1,4-diazepane, 2,5-diazabicyclo[2.2.1]heptane) and wherein L is selected from the group consisting of the group 2, 13 and 14 of claim 8 (1,2,4-triazolyl group).

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39. claims: 1-9,11,18,21-32,34,36,39,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by a C-N bond to form a N-containing ring system, (e.g. piperazine, 1,4-diazepane, 2,5-diazabicyclo[2.2.1]heptane) and wherein L is selected from the group consisting of the 3rd and 4th group of claim 8 (1,2,3-benzotriazolyl group).

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40. claims: 1-9,11,18,21-32,34,36,39,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by a C-N bond to form a N-containing ring system, (e.g. piperazine, 1,4-diazepane, 2,5-diazabicyclo[2.2.1]heptane) and wherein L is selected from the group consisting of the group 5 or 24 of claim 8 (pyrazolyl group).

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41. claims: 1-9,11,18,21-32,34,36,39,44-46 (all partially)

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by a C-N bond to form a N-containing ring system, (e.g. piperazine, 1,4-diazepane, 2,5-diazabicyclo[2.2.1]heptane) and wherein L is selected from the group consisting of the group 6 or 17 of claim 8 (imidazolyl group).

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42. claims: 1-9,11,18,21-32,34,36,39,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by a C-N bond to form a N-containing ring system, (e.g. piperazine, 1,4-diazepane, 2,5-diazabicyclo[2.2.1]heptane) and wherein L is selected from the group consisting of the group 7, 8, 10 or 12 of claim 8 (Y-N=CRa1-H, Y-N=CRa1-Cl, Y-NCRa2CH=CHRa1, Y-N=CRa1Ra2).

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43. claims: 1-6,8-9,11,18,21-28,30,32,34,36,39,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by a C-N bond to form a N-containing ring system, (e.g. piperazine, 1,4-diazepane, 2,5-diazabicyclo[2.2.1]heptane) and wherein L is selected from the group consisting of the group 9 of claim 8 (indol-1-yl group).

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44. claims: 1-6,8-9,11,18,21-28,30,32,34,36,39,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by a C-N bond to form a N-containing ring system, (e.g. piperazine, 1,4-diazepane, 2,5-diazabicyclo[2.2.1]heptane) and wherein L is selected from the group consisting of the group 11 of claim 8 (3H-benzo(d)-1,2,3-triazin-4-one-3-yl group).

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45. claims: 1-9,11,18,21-32,34,36,39,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by a C-N bond to form a N-containing ring system, (e.g. piperazine, 1,4-diazepane, 2,5-diazabicyclo[2.2.1]heptane) and wherein L is selected from the group consisting of the group 15 and 16 of claim 8 (1,2,3-triazolyl group).

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

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46. claims: 1-9,11,18,21-32,34,36,39,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by a C-N bond to form a N-containing ring system, (e.g. piperazine, 1,4-diazepane, 2,5-diazabicyclo[2.2.1]heptane) and wherein L is selected from the group consisting of the group 18 and 19 of claim 8 (pyrrolyl group).

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47. claims: 1-9,11,18,21-32,34,36,39,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by a C-N bond to form a N-containing ring system, (e.g. piperazine, 1,4-diazepane, 2,5-diazabicyclo[2.2.1]heptane) and wherein L is selected from the group consisting of the group 20, 21, 22, 23 of claim 8 (tetrazolyl group).

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48. claims: 1-9,11,18,21-32,34,36,39,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by a C-N bond to form a N-containing ring system, (e.g. piperazine, 1,4-diazepane, 2,5-diazabicyclo[2.2.1]heptane) and wherein L is selected from the group consisting of the group 25, 26 of claim 8 (tetrahydro- 1,2,3,4-isoquinolin-7-yl )(benzimidazol-2-yl, benzothiazol-2-yl-, benzoxazol-2-yl, 3H-indol-2-yl group).

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49. claims: 1-6,8-9,11,18,21-28,30,32,34,36,39,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by a C-N bond to form a N-containing ring system, (e.g. piperazine, 1,4-diazepane, 2,5-diazabicyclo[2.2.1]heptane) and wherein L is selected from the group consisting of the group 31-34 of claim 8 (benzimidazol-2-yl, benzothiazol-2-yl-, benzoxazol-2-yl, 3H-indol-2-yl group).

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50. claims: 1-9,11,18,21-32,34,36,39,44-46 (all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by a C-N bond to form a N-containing ring system, (e.g. piperazine, 1,4-diazepane, 2,5-diazabicyclo[2.2.1]heptane) and wherein L is selected from the group consisting of the group 35-37 of claim 8 (benzisoazol-1-yl, benzisothiazol-1-yl, 3H-isoindol-1-yl group).

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51. claims: 1-6,8-9,11,18,21-28,30,32,34,36,39,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by a C-N bond to form a N-containing ring system, (e.g. piperazine, 1,4-diazepane, 2,5-diazabicyclo[2.2.1]heptane) and wherein L is selected from the group consisting of the group 38, 39 or 40 of claim 8 (pyridinyl group) and the benzocondensed derivatives thereof as far .

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52. claims: 1-6,8-9,11,18,21-28,30,32,34,36,39,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by a C-N bond to form a N-containing ring system, (e.g. piperazine, 1,4-diazepane, 2,5-diazabicyclo[2.2.1]heptane) and wherein L is selected from the group consisting of the group 41, 43, 45 of claim 8 (pyrimidin-2-yl, pyrimidin-3-yl or pyrimidin-4-yl).

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53. claims: 1-6,8-9,11,18,21-28,30,32,34,36,39,44-46 (all partially)

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by a C-N bond to form a N-containing ring system, (e.g. piperazine, 1,4-diazepane, 2,5-diazabicyclo[2.2.1]heptane) and wherein L is selected from the group 42 and 44 of claim 8 (pyridazin-yl group).

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54. claims: 1-6,8-9,11,18,21-28,30,32,34,36,39,44-46 (all partially)

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Pharmaceutical composition comprising a compound of formula I and uses according to claims 1-26 wherein R1 is covalently bound to R2 by a C-N bond to form a N-containing ring system, (e.g. piperazine, 1,4-diazepane, 2,5-diazabicyclo[2.2.1]heptane) and wherein L is heteroaryl or heterocyclyl not provided for in inventions 38-53.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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Continuation of Box I.2

Claims Nos.: -

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible.

Present claims 1-46 relate to an extremely large number of possible compounds/uses. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a small proportion of the compounds/uses claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Present claims 1-26 relate to a compound/use defined

by reference to the following parameters/expressions:

a hydrolysable group, wherein pKa of the group L is as specified in claim 21, inhibition of the lipolytic activity of hormone-sensitive lipase against triacylglycerols, diacylglycerols, cholesterol acyl esters or steroid acyl esters, and disorders where it is desirable to inhibit the lipolytic activity of hormone-sensitive lipase against triacylglycerols, diacylglycerols, cholesterol acyl esters or steroid acyl esters; any disorder where it is desirable to modulate the plasma level of free fatty acids, glycerol, LDL-cholesterol, HDL-cholesterol, insulin and/or glucose and/or to modulate intracellular triacylglycerol, cholesterol ester stores, intracellular levels of fatty acids, fatty acid esters such as diacylglycerols, phosphatidic acids, long chain acyl-CoA's, as well as citrate or malonyl-CoA; and or increase insulin sensitivity in adipose tissue, skeletal muscle, liver or pancreatic beta cells, and or modulate insulin secretion from pancreatic beta cells, abnormalities of lipoprotein metabolism.

The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible.

Consequently, the search has been restricted to pharmaceutical

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

compositions comprising the individual compounds of the description as far as relating to invention 1, and their use in relation to the treatment of diabetes type 1, diabetes type 2, metabolic syndrome X, dyslipidemia, hyperglycemia and obesity.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

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